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TUBERCULOUS INFECTION AMONG NURSES AND MEDICAL STUDENTS IN SANATORIUMS AND GENERAL HOSPITALS

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THE fear of contagion from tuberculosis among medical workers is far from recent. Valsalva, who lived from 1666 to 1723, avoided autopsies of those dying from phthisis, because he was afraid of contracting the disease. Morgagni did likewise to protect himself and his pupils from exposure. Laënnec, who died from tuberculosis, was convinced that he had acquired his illness while doing post-mortem examinations. In the middle of the last century, French army surgeons had already observed the high incidence of tuberculosis among the orderlies of the military hospitals in times of peace.

These clinical observations were to receive their scientific confirmation in 1865, when Villemain recognized the transmissibility of tuberculosis, and their undeniable proof in 1882, when Koch announced to the world the discovery of the tubercle bacillus. In that year, pulmonary tuberculosis entered automatically into the rapidly growing class of contagious diseases.

The medical profession, however, was slow to adopt a logical attitude toward the adequate protection of all those entrusted with the care of tuberculous patients. Not that some of its members were not aware of the possibilities of infection. On the contrary, as early as 1889, Cornet[1] reported on the epidemiology of tuberculosis in the German Catholic nursing orders for twenty-five years and found the death rate from that disease exceedingly high, especially among the young nuns. "A girl of seventeen," he wrote, "devoting herself to hospital nursing died on the average twenty-one and a half years sooner than a girl of the same age moving among the general population." Tuberculosis was responsible for 63 per cent of the total deaths among these nursing nuns. This appalling mortality is understandable if one remembers that Cornet's survey covered the period from 1864 to 1889, most of which was prior to the discovery of Koch's bacillus and even to the Pasteur era.

This warning stirred no response until 1910, when Hamel,[1] at the suggestion of Koch, inquired from 549 German institutions admitting tuberculous patients as to the morbidity from tuberculosis among their personnel. The survey included 2861 physicians and 14,140 nurses for the years 1906 to 1910. The rate of infection among them was found to be practically the same as that among the general population. This was in direct contradiction of Cornet's report.

Dublin,[2] commenting on these figures, pointed out that the factors of age and duration of employment were not taken into account and that the reluctance of some of the nuns to submit to examination let a good many cases go unrecognized. Hamel's findings were, nevertheless, a long way from those of Cornet, and Dublin considered himself justified to conclude:

> In view of the German figures and the personal experience of those who have long carried on America's tuberculosis work, more and more physicians and nurses should find themselves ready to enter this field of social service without the fears, usually present, of possible infection. With proper precautions taken, adults can engage in this work with well-nigh perfect immunity.

The "proper precautions," up to the last few years, meant the hygienic disposal of the sputum. Recent events lead one to believe that this has been inadequate.

Dublin based his opinion on no less an authority than Trudeau, who wrote in a personal letter:

> In the early days of the sanatorium, and for the past ten years, many of our employees, dining room maids and so forth were, as far as I know, healthy people. To my knowledge, none of these ever developed tuberculosis at the sanatorium.

*Read before the Worcester District Medical Society, October 9, 1940.

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The most authoritative American teachers and writers on the subject were then voicing a similar opinion. "Infection almost never occurs in sanatoria where the proper precautions are taken," Pottenger[3] stated in the 1908 edition of his book. That the same opinion was prevalent in England, Germany and the United States is implied by what he added:

> Although the Brompton Hospital, London, has treated more than 15,000 cases of tuberculosis during the past twenty years, yet, neither a nurse, a physician nor an attendant has become infected. The same record has been made in Falkenstein and Goerbersdorf, Germany, and in the Adirondack Cottage Sanatorium and Winyah in the United States. Here we have intimate association of patients and attendants for months and years with no infection occurring. We can safely say, then, that tuberculosis is only communicable when proper care is not used.

In 1917 he[4] expressed the same belief:

> The attendants of these institutions [sanatoriums and tuberculosis hospitals] instead of being prone to infection, seem to show even a smaller number of infections than occur in human beings generally.

Fishberg[5] goes farther in the same direction. He quotes numerous French and German authorities, among them Saugman, who claims, "It is not dangerous for healthy adults to be coughed at by patients suffering from pulmonary or laryngeal tuberculosis." "During the thirty years of the existence of the Montefiore Hospital," writes Fishberg, "no nurse, orderly or physician has been observed to have been infected while attending to the needs of the tuberculous patients." He concludes, "Such facts have been quoted to disprove the transmissibility of tuberculosis, but in the light of our present knowledge, they merely prove that reinfection is impossible."

In 1924, Clark[6] answered his own question, "Is caring for tuberculosis patients dangerous to the nurse?" by relating the experience of Aufrecht, who was unable to find a single case of infection among 263 nurses at the Madgeburg-Alstadt Hospital, where 3828 tuberculous patients had been admitted during the period 1880 to 1897, and that of Brunon, who studied the records of the Rouen hospitals for thirty years and found that nurses and attendants died of tuberculosis less often than the general population of that city.

In 1931, Fishberg[7] endeavored to refute an article of Myers,[8] and claimed to "know of no evidence that the incidence of tuberculosis in medical students is higher than that of other young men and women." In 1940, Brahdy[9] concluded an article with the statement that: "The incidence of tuberculosis among hospital personnel is about the same as that in any similar group." He makes an exception for nurses, whose higher rate of infection he attributes to their being tuberculin negative on entrance to the hospital.

The preceding quotations explain the impression prevailing among a good many to this day that a contact such as that of nurse to patient carries no danger of infection from tuberculosis.

From 1925 on, however, a decided change appeared in the figures and in the tone of the articles on this subject. Britton and Bollman[10] and Shipman and Davis,[11] in this country, and Kirchner[12] and Mücke[13] in Germany found the incidence of tuberculosis to be much higher among nurses than in the same age group in the community. Heimbeck,[14] of the Oslo General Hospital, claimed in 1928 that 50 nurses out of 420, that is, almost 1 out of 8, developed tuberculosis in the course of their training. Reports of high morbidity rates from tuberculosis among interns, nurses and orderlies poured in from everywhere: 4.5 per cent, according to Fisher,[15] of California; 29.1 per cent for one class of nurses at the Macon County Sanatorium, Illinois[16]; and 3 per cent in the New Zealand base hospitals.[17] Geer[18] found from 4.5 to 5.5 per cent at the Ancker Hospital, St. Paul, Minnesota, and Hedvall[19] 5.3 per cent in probationary nurses at the Lund University Hospital in Sweden. Boynton[20] declared in 1939:

> The tuberculosis infection rate is a hundred times greater in the student nurses on a general hospital service than in the students of the College of Education and five hundred times greater in student nurses on a special tuberculosis service than in the College of Education students.

Her study was carried out at the University of Minnesota Hospital.

Cases of infection of medical students have also come to the attention of epidemiologists. A wealth of material has been accumulated in various medical schools, in this country and abroad, showing that the rate of morbidity from tuberculosis among the second, third and fourth year medical students is generally greater than that among other young men and women of the same age group. Myers's[21] first conclusion in an article written in 1933 was, "The incidence of tuberculosis among students and recent graduates of schools of nursing and medicine is so high that the disease may be looked upon as a serious menace to professional health workers." In 1939, Soper and Amberson[22] surveyed the literature and gave their own figures in a comprehensive report. They noted an incidence of tuberculosis of 5.8 per cent among the medical students at the University of Pennsylvania in 1935–1936, decreasing gradually to 3.7 per cent in 1937–1938. Dr. Heath, of Harvard Medical School, wrote to Dr. Soper in 1938, "There

is no doubt that tuberculosis is the most important organic medical problem in the medical school." According to Soper and Amberson, however, Stanford University had only 1.0 per cent, Johns Hopkins 1.4 per cent, Yale a little more than 1 per cent and Columbia 0.4 per cent.

The incidence is higher abroad: Scheel[23] gives 2.3 per cent for the Oslo Medical School. The most recent and at the same time one of the most interesting reports comes from Lund University, Sweden, where Hedvall[19] gives the figures listed in Table 1. This rate of infection

TABLE 1. *Incidence of Tuberculosis in the Different Faculties.*

FACULTY	NO. OF PERSONS EXAMINED	NO. OF CASES OF TUBERCULOSIS FOUND	TUBERCULOSIS IN DIFFERENT GROUPS
			%
Medical students	638	72	11.3
Philosophy students	1367	17	1.2
Theology students	409	12	2.9
Law students	488	9	1.8
Probationary nurses	434	23	5.3

among medical students is about the highest officially reported. The most enlightening part of Hedvall's report is the tracing of the main source of infection to the autopsy room. Samples from towels, trays and tables taken twenty-four hours after a necropsy examination contained tubercle bacilli on cultures, in spite of all precautions during the post-mortem procedure.

That the danger of contamination from this source may be serious is demonstrated by the following data obtained from various hospitals in Massachusetts. In 3766 post-mortem examinations at the Boston City Hospital in the years 1935–1939 inclusive, tuberculosis was found to be the primary or contributory cause of death in 285 cases, that is, at the rate of 7 per cent. Fourteen out of 236 cases, or 6 per cent, were reported from the Worcester State Hospital for 1937 and 1938. In the same years the Worcester Hahnemann Hospital had 3.8 per cent, the Worcester Memorial Hospital (Worcester) 2.7 per cent and St. Vincent Hospital (Worcester) 1.5 per cent. From the Worcester City Hospital comes the surprisingly low figure of 0.9 per cent for the years 1934–1938 inclusive. At the Buffalo General Hospital and Children's Hospital, Terplan[24] reported that the incidence of tuberculous lesions at autopsy of about 700 children and young adults was 5.9 per cent in those younger than seven years of age and 19.4 per cent in those between seven and eighteen.

The percentage of tuberculous foci found in the autopsy room of general hospitals indicates that there may be more lesions in their wards than one would suspect. Badger and Spink[25] noted an annual average of 634 tuberculous patients admitted to the general wards of the Boston City Hospital from 1930 to 1934 inclusive. Ten per cent of the deaths from tuberculosis occurred in the general hospitals of upstate New York in 1936–1937,[26] and 20 per cent in the general hospitals of Massachusetts in 1939. Of 65,000 deaths from tuberculosis in the United States in 1933–1934, 5306 (7 per cent) occurred in tuberculosis departments of general hospitals.[27] In a recent x-ray survey of 4853 patients admitted at fifteen representative general hospitals, Plunkett and Mikol[28] found 2.6 per cent with pulmonary tuberculosis. This explains some seemingly paradoxical reports of higher incidence of tuberculosis among general-hospital nurses than among nurses at tuberculosis sanatoriums. There is less contact in the former institutions, no doubt, but that contact becomes more dangerous because it is unrecognized and because no precautions are taken.

EXPERIENCE AND EXPERIMENTS

My observations have paralleled the experience of those who have noted a high morbidity rate among their nursing personnel. From 1926 to 1936 inclusive, out of 174 healthy pupil nurses on admission to training, 16 developed tuberculous lesions demonstrable by x-ray, a morbidity rate of 9.2 per cent. They were all between the ages of eighteen and twenty-one. Of the 11 that were skin tested by the Mantoux method, 6 reacted positively, and 5 negatively. Four developed pleural effusions that cleared up spontaneously. Twelve showed parenchymatous lesions, but 8 of these never went beyond the minimal stage. Six had positive sputum. Fourteen took rest treatment for some time, varying between a few months to a year. Two refused to do so. Six received pneumothorax and one a phrenicectomy. Fourteen are now well. One is ill. One, who had been in contact with a tuberculous brother before entering the school, died. Three of the 16 nurses became ill from two to five years after they had left Rutland, and so far as they are concerned, the training school might well plead not guilty if it wished to do so. This would bring the morbidity rate down to 7.5 per cent.

To prevent further contagion, I have tried to determine the likeliest points of contamination in the immediate surroundings of the patients. The sputum is collected in a thick, oilpaper container and burned. This presents no difficulty. The droplets projected during coughing spells constitute the main problem. In spite of repeated instructions, some patients, because of thoughtlessness, neglect or lack of strength, fail to cover their mouths. Particles of sputum and saliva float

in the air for a short while and fall on the bedcovers, on the pillows and on the bedside tables, and may even reach the wall next to the bed. Other patients cover their mouths with their hands and contaminate the objects that they handle. One may easily judge from this that the dangers of infection vary greatly according to the habits and to the degree of illness of each person.

Cultures of tubercle bacilli were grown from the sterile water used to wash the bed sheets, the table, the walls and the floor of a room in which a particularly untidy patient had died the day before. The same procedure, repeated after the ordinary routine cleaning, — washing of walls, woodwork, floors, bedstead, table and chairs with soap and water, — still gave a positive result from the wall wash, but a negative one from the table and the floor washes. The experiment was carried out in several other rooms, with negative results. The sediment obtained from three floor sweepings in another room infected a guinea pig. No organisms grew from doorknob washes and from a basin of water kept on the bedside table of a very ill patient for twenty-four hours. No tubercle bacilli could be recovered from nose swabs of nurses returning from duty in the sickrooms or from the sterile water in which their masks had been left to soak after use.

The small scale on which these experiments were carried out detracts in no way from their value. They prove that tubercle bacilli are present in the immediate vicinity of tuberculous patients, and that their number increases with the stage of the disease, the severity of the cough and the lack of precaution taken by the patient.

Discussion

The belief of the oldest observers, Valsalva, Morgagni, Laënnec and Villemain, after being partially disregarded by the medical writers of the early nineteenth century, has thus been exhumed and established on a solid foundation of facts and figures during the last ten or twelve years. The reason lies in the fact that the period from 1925 to 1940 has been illuminated by the light of the x-ray. There is no doubt that the morbidity from tuberculosis was probably as high in the twenty-five preceding years, but it could not be recognized clinically in time to be associated with the source of infection. The invasion of the lungs by the bacillus took place silently, without outward manifestations, or under the disguise of colds, grippes, influenzas and so forth, as it often does even today. It receded spontaneously in many cases or smoldered during the years of training to flare up later when the nurses had left the hospital and had been lost to sight.

Skin testing has been an even more sensitive gauge than the x-rays to determine the rate of infection in nurses and students. Of 126 nurses tuberculin tested at the Boston City Hospital, 60 per cent were positive on entering the school, and 90 per cent after their three years of training.[29] Of 70 student nurses negative to tuberculin at the beginning of their training, all but 10 were positive at the end, according to Amberson and Riggins.[30] Most of the reports show similar figures.

It is also possible that the increase in the incidence of tuberculosis noted during the last decade may be due, in part, to the enormous amount of study required from student nurses. Added to the work, the weight of this adverse factor may be sufficient to tip against them the sensitive scale in which their acquired resistance would otherwise counterbalance repeated exposures.

Much has been said and written on the question of allergy, and much confusion has resulted. On one point, most observers agree. The number of lesions recognizable by x-ray study and the number of clinical infections are far greater among the tuberculin-negative reactors than among the positive ones. This led some European and Canadian clinicians to immunize the former group by means of BCG. Among others, Heimbeck's[31] statistics point to a remarkable degree of protection resulting from the use of this vaccine.

Conclusions

It seems generally accepted that the danger of contracting tuberculosis constitutes a serious hazard for young persons entering training school, and to a lesser degree, for medical students. This being so, the logical move is toward prophylaxis, and the following preventive measures are suggested:

No nurse, orderly or wardmaid should be permitted to work in a sanatorium before the age of twenty-one.

The affiliation of nurses to sanatoriums from general hospitals should be postponed to the third year of training.

The diet should be sufficient and well balanced. The work should not be too hard nor the hours too long. The living quarters should be spacious and well aerated. A false economy has often inspired shortsighted policies in regard to the three preceding items. The compulsory eight-hour day in state hospitals is commendable. A month's vacation a year is desirable.

All nurses should be skin tested, x-rayed, weighed and examined on admission and every four to six months during their training.

Vaccination of the tuberculin-negative reac-

tors by means of BCG is current practice in many European hospitals, and it seems to offer considerable protection. Medical opinion in this country is not yet prepared for the adoption of this protective measure.

Nurses should wear gauze masks of sufficient thickness while taking care of patients with open tuberculosis, especially while making beds and giving baths. They should be instructed not to shake the blankets, pillow-cases, bathrobes and so forth. They should be careful to wash their hands as soon as they are through with one patient, and to change their uniforms before leaving the ward. The soiled linen should be collected in bags and sent immediately to the laundry. The bags should be emptied directly into the washer with as little handling as possible.

All dishes, trays, glasses and so forth should be sent to the central dishwasher and sterilized by live steam. (Recent advances in the utilization of ultraviolet rays offer hope for their practical application in the field of hospital disinfection.)

Patients must be instructed not to cover their mouths with their hands, when coughing, but with paper napkins, which are thrown into paper bags pinned to the bedside tables.

In general hospitals, an effort should be made to detect patients suffering from pulmonary tuberculosis. If the cost of a routine chest film is considered too high, that of a fluoroscopic examination is negligible. The efficiency of the screen does not equal that of the film, but it is 80 per cent better than that of the stethoscope and 100 per cent better than no chest examination.

Where these or similar measures have been enforced, the rate of infection among nurses and hospital personnel has been brought below that of the general population.

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HEMATOMA OF THE BRAIN*

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THE formation of a large localized hematoma within the substance of the brain is rather uncommon. The term, "hematoma of the brain," is used so that the pathologic condition under discussion may be strictly limited to large circumscribed collections of extravasated blood that are completely within the brain substance. Petechial or very small hemorrhages, massive cerebral hemorrhages rupturing into the ventricles or subarachnoid space and all circumscribed hematomas secondary to brain neoplasm are excluded from consideration. The fact that most hematomas of the brain produce signs and symptoms resembling the syndrome of an expanding intracranial neoplasm and that many of them respond well to surgical treatment is, perhaps, not generally appreciated. Comparatively few reports of such lesions that have been operated on can be found in the literature.

Four cases of hematoma of the brain have been collected from the records of the Neurological Institute during the last fifteen years, and in all cases surgical treatment was successful. In every case the hematoma was intracerebral and the preoperative diagnosis was either neoplasm or abscess.

CASE REPORTS

CASE 1. (N. I. 11910) N. M., a 59-year-old man, was admitted to the Neurological Institute on March 21, 1932, complaining of speech difficulty, occasional frontal headache and slight vertigo. The onset of his illness was 1 month before admission. In the evening, while playing cards and without any warning, he suddenly became unable to speak or to call names, and reeled on attempting to walk. The next day he was confused and spoke in a jargon, but at no time was he unconscious. He vomited on this day. He was admitted to a hospital, where an operation "through his nose" revealed pus. Two or three months prior to admission, he had noticed a momentary aphasia; he could not call the names of the stations while working as a subway guard. His son said that he had noted this difficulty in calling names about two years previously. He had never had a convulsion.

The patient was a well-built, vigorous man with a blood pressure of 160/90. There was a moderate arteriosclerosis, the heart was slightly enlarged, and the sounds were somewhat indistinct. There were a few transitory rales and a slight emphysema. The olfactory sense was poor on both sides. The optic disks were blurred, and there was a right homonomous hemianopia. The pupils were sluggish to light. There was a right hyper-reflexia, and a nominal aphasia. The diagnosis on admission was a left-temporal-lobe neoplasm.

Examination of the blood revealed a red-cell count of 4,500,000 with a hemoglobin of 81 per cent, and a white-cell count of 9100, with a normal differential. The blood and spinal-fluid Wassermann reactions were negative, and the blood chemical findings normal. The first spinal fluid showed a + test for globulin, 75 mg. per 100 cc. total protein and 4 lymphocytes per cubic millimeter. Two subsequent fluids had negative globulin reactions; the total protein was 37 and 21 mg. per 100 cc., and lymphocytes numbered 18 and 2, respectively. The urine was normal. X-ray examination of the skull showed no disease; the pineal gland was not visualized. The various diagnoses considered were: left-temporal-lobe neoplasm; thrombosis of the left lenticulostriate artery; single acute hemorrhage of the brain (branch of the left mid-cerebral artery). Encephalography revealed a shift to the right of the lateral and third ventricles. The hippocampal recess was present on the right but absent on the left side, and the left temporal horn was only partially outlined. The findings were considered to indicate a left frontotemporal tumor.

The patient was transferred to the surgical service, where a preoperative diagnosis of a left temporal meningioma was made. A left temporal osteoplastic flap was turned down by Dr. Byron Stookey. On the cortex of the temporal lobe was an area, about 5 cm. in diameter, that showed an increased vascularity. The upper gyrus of the temporal lobe, for a space of 2 or 3 cm., was almost canary yellow, whereas the surrounding gyri were quite white. A cannula was passed through the yellow degenerated area, and no fluid was found. On incision, a massive blood clot was found at a depth of 2 cm. Microscopic examination of the fresh tissue, including sections from the adjacent brain substance, was reported as "hemorrhage into degenerated tissue." The clot, which measured 2 by 3 by 2 cm., was removed, the edges of the cortex were allowed to come together, and the dura was closed. The pathological report showed that the tissue was composed of an edematous glial mat in which there were many compound granular cells containing hemosiderin, fat and masses of red cells. The diagnosis was: zone of reaction about an old cerebral hemorrhage.

The patient had a prompt recovery, and when he was discharged on May 10, 1932, aphasia was still present. The follow-up examination on August 2, 1933, showed that the aphasia persisted to a moderate degree. When he was last seen on August 2, 1934, two and a half years after operation, his condition was normal except for a mild nominal aphasia.

CASE 2. (N. I. 29949) L. P., a 15-year-old girl, was admitted to the Neurological Institute on August 23, 1936, complaining of headache, poor vision, nausea and vomiting. Two years before admission she had a generalized convulsion; previous to this she had frontal headaches and poor vision. Nine days before admission she began to have a left-sided headache, drowsiness, photophobia and nausea. The drowsiness increased, and the patient was

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admitted in stupor. There was no history of trauma.

Examination revealed a well-nourished girl who was drowsy and appeared acutely ill. There was a right lower facial weakness, the right abdominal reflexes were absent, and all the deep reflexes were absent except the right ankle jerk, which was increased. There was a right Babinski reaction. The fundi showed 1 to 2 diopters of papilledema on the right, and 4 to 5 diopters on the left. Pinprick was felt better on the left, and the patient moved the left extremities more freely than the right. The admission diagnosis was a left temporal neoplasm.

Examination of the blood showed a red-cell count of 4,280,000 with a hemoglobin of 78 per cent, and a white-cell count of 13,450 with 87 per cent polymorphonuclears. The blood Wassermann reaction was negative, and the urine normal. X-ray studies of the skull showed that the left middle meningeal channels were slightly larger than the right.

On August 24, 1936, a left osteoplastic flap was turned by Dr. Fritz J. Cramer. Just under the tense dura a soft area was found in the center of the exposure. A needle was inserted to 4 cm., where a definite resistance was felt; the needle was forced deeper and about 25 cc. of dark, bile-colored fluid was obtained. The dura was then opened widely. The exposed cortex showed wide, yellow gyri and a narrowing of the sulci, giving the impression of an underlying glioma. An incision was made in the posterior portion of the superior temporal gyrus; at a depth of 3 cm. a large collection of old clotted blood was found. Several small, cystlike collections of clot were also found, and the impression was gained that the lesion was lobulated. A specimen was taken from the wall and also from the yellow cortex. The surgeon stated that there were two hematomas, one about to rupture and one deeper and more solid. The pathological report was: one old and one recent hemorrhage in the cerebrum.

The postoperative course was uneventful, and when the patient was discharged on September 5, 1936, she still had an unsteady gait and hyporeflexia.

In the summer of 1937, the patient had a recurrence of the original symptoms, but without any disturbance of consciousness. Repeated examinations disclosed only a slight increase of the deep reflexes on the right side and some suppression of associated movements on the right. Needle exploration in the region of the former hematoma showed no blood or fluid, and a ventriculogram revealed very slight evidence of a space-occupying lesion on the left. The patient slowly improved and left the hospital in good condition. She has been followed for three and a half years, and there has been no essential change in her condition.

Case 3. (N.I. 36399) A. M., a 34-year-old woman, was admitted to the Neurological Institute on January 4, 1938, in a semistuporous condition. She was found in this condition by her husband on December 29, 1937. She was unable to talk, but she could be aroused by stimulation; it was noted that she had a marked weakness of the right arm and leg. Her condition did not improve and, after 3 days, she was sent to a hospital; on the following day she was admitted here. In 1923 she had been struck by a taxi; she was unconscious for 24 hours and was in bed for 3 months. A hysterectomy and an oöphorectomy were performed in 1935. Not long after this, the patient became critical of those around her. She was untidy, forgetful and, at times, appeared dazed. In January, 1936, 2 years before admission, her husband found her in a semistupor; she was unable to walk or talk, but appeared to be as well as usual on the following morning. In March, 1937, she was again found in the same condition; on recovery she complained of weakness of the right arm for several weeks.

Examination revealed a complete right hemiplegia, including the face, with all concomitant signs. The patient could not form words and understood very little that was said to her, but on repeated commands she could perform simple acts. Sensation was diminished on the right side. The right pupil was slightly larger than the left, but both pupils reacted to light and accommodation. The fundi showed a high degree of myopia and slight papilledema. The admission diagnosis was a left frontal neoplasm.

The blood count, urinalysis and blood Wassermann reaction were normal. The spinal-fluid pressure was 420 mm. of water; the fluid was xanthochromic and contained 66 lymphocytes per cubic millimeter and 220 mg. of protein per 100 cc., and gave a +++ test for globulin. The gold-sol curve was normal. X-ray examination of the skull showed moderate atrophy of the posterior clinoids and dorsum sellae.

On January 7, a ventriculogram showed evidence of a tumor in the left posterior frontal region. The patient was returned to the operating room, and a left fronto-parietal flap was turned under local anesthesia by Dr. Byron Stookey. A large hematoma was found deep in the brain at the middle portion of the mid-frontal and ascending frontal convolutions. The clot extended to a depth of 4 or 5 cm. and was surrounded by degenerated brain tissue. The pathological report of the tissue removed at operation was: encephalomalacia and recent hemorrhage into the brain substance.

The patient gradually became brighter and tried to talk. She slowly regained the use of the right lower extremity. She was discharged on February 23, when she could walk quite well, but the right arm was still spastic and the aphasia was still present. Re-examination in February, 1940, showed an improvement in the aphasia; the patient could walk for a considerable distance. During the last two years, she has had occasional convulsions.

Case 4. (N. I. 41189) H. F., a 47-year-old man, was admitted to the Neurological Institute on February 28, 1939, with fever and delirium. Three weeks before admission the patient had a chill, with fever and aching muscles. On the next day he complained of severe headache over the left frontal area; he had a temperature of 101°F. and a rapid pulse. Since then he had had a dull, left-sided headache, but after one week, he returned to work, although he was drowsy and depressed. On February 20, he was unusually drowsy and acted strangely. Instead of going to work, he confabulated with his wife and sneaked back to bed. In the afternoon he went to his club and borrowed $50 for no good reason. While there he had his first visual complaint; he bumped into things, and he could not read. He had no diplopia but had marked dizziness, and he could not sign his check. After returning home he had projectile vomiting for the rest of the day and night. This was accompanied by a left-sided headache that soon became very severe.

On admission the patient was delirious, unco-operative and under heavy sedation; the temperature was 104°F. He had a pyknic habitus and was obese. The chest was normal. He was unable to walk, but had no demonstrable muscular weakness. The deep reflexes were hypotonic, and there was no Babinski reaction. Sensation was normal. The disks could not be seen well; the pupils reacted to light and accommodation; there was some

TABLE 1. *Summary of Cases Reported in the Literature.*

AUTHORITY	AGE	SEX	ETIOLOGIC FACTORS	INITIAL SYMPTOMS	CLINICAL COURSE	OPERATION	LOCATION OF HEMORRHAGE	OUTCOME
	yr.							
Cushing[4] (1903)	40	M	Trauma, high blood pressure	Unconsciousness	Thirty-six hr. later developed right hemiplegia; B. P. 300; P. 50.	Craniotomy and puncture	Left frontoparietal	Recovered, died later
Russell and Sargent[5] (1909)			Hypertension	Unconsciousness	Right hemiplegia and aphasia	Craniotomy	Left frontoparietal	Recovered
Naffziger and Jones[2] (1928)	42	M	Trauma	Unconsciousness (short)	Progressive to coma 24 hr. later	Craniotomy and incision	Right temporal (large)	Recovered
	62	M	Trauma	Unconscious (10 hr.)	Progressive to coma; 42 hr. later had sudden hemiplegia.	Craniotomy	Right temporal	Recovered
	30	M	Trauma	Next day had headache	Gradual onset of intracranial pressure; 18 days later had hemianopia.	Craniotomy	Right temporal (deep)	Recovered
Bagley[6] (1932)	48	M	Arterio-sclerosis	Focal convulsions (2 yr.)	Gradual stupor and hemiparesis; aphasia and papilledema 16 days later.	Craniotomy and incision	Left temporoparietal (extensive)	Died
	39	F	None	Sudden headache	Next day stupor; progressed to coma on 6th day; papilledema but no definite paralysis.	Craniotomy and incision	Left frontoparietal (extensive)	Recovered, died 10 days later
	49	M	Syphilis?	Slowly became drowsy and confused	Gradual stupor; papilledema and sudden hemiparesis on 14th day, and worse on 20th day; B. P. 210/55.	Craniotomy	Left temporal (too large to remove)	Died 24 hr. later
	43	M	None	Sudden headache and confusion	Gradual progress; developed signs of left cortical lesion and hemianopia; worse on 12th day.	Craniotomy and aspiration (30 cc.)	Left frontal	Recovered
	35	M	None	Sudden hemiparesis, stupor	Progressive to coma and complete hemiplegia; critical on 12th day.	Craniotomy and aspiration (40 cc.)	Temporal	Second operation 5 mo. later, recovery
	34	M	None	Sudden headache and hemiparesis	Gradual progress until on 19th day developed coma and complete hemiplegia	Right temporal decompression	No hematoma found (probably present)	Recovered
Penfield[7] (1933)	14	M	Initial smoking	Vomiting	Unconscious soon; 5 days later had aphasia and right hemiplegia.	Craniotomy and incision	Left temporal	Recovered
	40	F	Hypertension	Dizziness and diplopia	Soon had right hemianesthesia, hemiparesis and hemianopia; aphasia on 3rd day.	Craniotomy and incision	Left occipital	Recovered, sudden death 6 mo. later
de Lauwereyns[1] (1934)	?	M	Trauma	Concussion and confusion	On 4th day had right hemiparesis and headache; increasing stupor; P. 52 on 11th day.	Craniotomy and evacuation (20 cc.)	Left parietal	Recovered
	15	F	Trauma	Unconscious short time	Gradual paresis and anesthesia of left forearm; became critical on 14th day.	Trephine and puncture	Right parietal	Recovered
	52	F	Trauma	Semicoma, right hemiparesis	Next day focal convulsions of face and arm; aphasia on 3rd day.	Craniotomy and evacuation (50 cc.)	Left frontoparietal	Recovered
	21	M	Trauma	Headache	In 3 days had facial paresis after drainage of extradural hematoma	Craniotomy and evacuation (15 cc.)	Left frontoparietal	Recovered
	28	M	Trauma	Short loss of consciousness	Rapid progress to coma in 8 hours with facial paresis	Trephine and puncture	Left frontal	Recovered

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	?	?	Trauma	Short loss of consciousness	Free interval; then aphasia and right hemiplegia developed.	Pieces of bone removed	Left frontal	Died
	35	M	Trauma	Headache	Gradual onset of left hemiparesis	Not completed	Right temporo-occipital	Died
	?	M	Trauma	None	Gradually developed poor vision and headache; sudden coma after 8 days.	None: waited too long	Right temporal (just ruptured)	Died
	25	M	Trauma	Head laceration	Next day paresis of right arm; worse on 12th day.	Craniotomy, extracerebral and intracerebral	Right frontoparietal	Recovered
Craig and Adson[8] (1936)	18	M	Trauma	Dazed and weak, poor vision	Headaches for 7 mo.; then convulsions and hemianopia.	Craniotomy and aspiration	Right temporo-occipital	Recovered
	39	M	Trauma	Dazed and weak 4 days	Three mo. later sudden headache, right paresthesia and aphasia; 1 mo. later focal attacks and papilledema.	Craniotomy and incision	Left parietal (encapsulated)	Recovered
	37	M	None	Headaches for 6 mo.	Vomiting and gradual right hemiparesis; in 6 wk. had aphasia and papilledema.	Craniotomy and incision	Left parietal (cystic)	Recovered
	20	F	Heart disease (*Str. viridans*)	Unconscious for 4 hr., 6 wk. previously	Later poor memory, hemianopia, papilledema and facial weakness; jocular.	Craniotomy and incision	Right temporoparietal	Recovered, death 3 mo. later from infection
	25	M	None	Unconscious for 20 min.	Three days later vomiting; headache and aphasia in 3 wk.	Craniotomy and excision	Left temporal	Recovered
	30	F	None	Numbness of hand	Soon right leg became numb; 4 days later right hemiparesis.	Craniotomy and incision	Left temporoparietal	Recovered
	46	M	None	Paresis of leg next morning	Next day arm weak; B. P. 125/80; x-ray showed expanding lesion.	Craniotomy and incision	Right parietal	Recovered
	62	M	Trauma (12 yr. previously)	Sudden blurred vision	Hemianopia, hemiparesis and paresthesia; B. P. 116/68.	Craniotomy and incision (75 cc.)	Right parietal	Recovered
	35	M	None	Headache for 2 days	Two days later sudden hemiparesis and numbness; stupor in 3 days more; papilledema; x-ray showed frontal lesion.	Craniotomy and incision	Left frontal	Recovered, suddenly died 9 days later
Kaplan[9] (1937)	57	F	Otorrhea (few years)	Headache and vomiting	In 5 days hemiplegia, aphasia, nystagmus and head turned to right; critical on 7th day.	Craniotomy and aspiration (50–60 cc.)	Internal capsule (deep)	Recovered
Doughty[10] (1938)	39	M	Hypertension and trauma	Headache	Two wk. later sudden focal attacks and hemiparesis	Craniotomy and incision	Right frontal	Recovered
	24	M	Trauma	Dazed	Two mo. later twitching of right face and hand; papilledema.	Craniotomy and incision	Left frontal	Recovered, second operation 4 mo. later
	16	M	Trauma	Numbness of right hand	Few days of headache and right paresthesia; 1 mo. later had hemiparesis and papilledema.	Craniotomy and incision	Left frontoparietal	Recovered
	24	M	Trauma	None	Four mo. later headaches; 2 wk. later 2nd slight trauma; vomiting and rapid development of coma.	Craniotomy	Left frontoparietal (extensive)	Died
Laruelle and Massion-Verniory[11] (1938)	25	M	Coryza (8 days)	Sudden headache and vomiting	Unconscious next day; then delirium and hemianopia; P. 60; x-ray showed no air in ventricles; worse on 12th day.	Craniotomy and evacuation by needle	Right frontoparietal (size of egg)	Recovered
Ecker and Love[12] (1939)	11	M	Trauma	Dazed	Mild headaches for 3 yr., becoming increasingly severe; then vomiting, diplopia and papilledema.	Craniotomy and aspiration (30 cc.)	Left frontal (3 cm. deep)	Recovered

disassociation of the extraocular muscles, and nystagmus was present on lateral gaze. He was disorientated and had delusions. The blood pressure was 150/90. The admission diagnosis was a right frontotemporal brain abscess.

Blood examination showed a red-cell count of 3,740,000 with a hemoglobin of 60 per cent, and a white-cell count of 11,350 with 86 per cent polymorphonuclears; achromia, polychromatophilia and anisocytosis were present. Examination of the urine showed a ++ test for albumin, a + test for glucose and a + test for bile, with a few red and white cells per high-power field, and some granular casts. The spinal fluid was clear and had 8 white-blood cells and 5500 red-blood cells per cubic millimeter; the total protein was 68 mg. per 100 cc., and there was a + test for globulin. Culture of the fluid was negative. X-ray examination showed questionable atrophy of the posterior clinoids and dorsum sellae and changes that suggested early Paget's disease.

The patient was transferred to the surgical service, where it was thought that he had a right frontotemporal brain abscess. On the day of entry a right temporal decompression was done by Dr. Clement B. Masson. Following this operation, the patient's condition improved somewhat. On March 11, an encephalogram revealed a mass involving the right occipital and parietal lobes. A left homonomous hemianopia was found by the eye consultant. On March 14, a right parietotemporal flap was turned down by Dr. Masson. The cortex over the parieto-occipital region was rather soft, and there was a small, yellow discolored area in the posterior part of the operative field. This was incised, and a large hematoma, about the size of a lemon, was found at a depth of 3 cm. in the posterior part of the parietal and the greater part of the occipital lobes. Evacuation was done, and the patient made an uneventful recovery. Pathological examination showed encephalomalacia and hemorrhage in the cerebrum.

The patient was discharged on March 30, with a slight improvement in his visual fields, and was otherwise apparently well. He had no complaints, except occasional feelings of "nervousness," until June 15, when he became unconscious and was said to have a blood pressure "over 280." During the subsequent 6 months, he had 3 similar attacks, each of which lasted 15 minutes. He was readmitted on January 3, 1940, with a diagnosis of paroxysmal hypertension; the blood pressure was 205/140. A bilateral splanchnic resection was done in two stages. Following this, the patient improved greatly and the blood pressure dropped to 150/90 and remained at this level until he was discharged on February 10.

Heusner, in 1888, first reported an intracerebral hematoma successfully treated by trephination and puncture — the second case in the series collected by de Lauwereyns.[1] Since then a study of the literature has revealed 36 proved cases treated by surgery and 1 probable case that was relieved by trephination only, Kron and Mintz[2] reporting the only case of an intracerebellar hematoma. The greater number of these cases were reported after Naffziger and Jones's[3] paper in 1928. Probably there are many unrecognized cases and some cases surgically treated but not reported. The essential points of the cases found in the literature are given in Table 1.

Etiology and Pathology

With the exception of those cases in which the signs and symptoms follow soon after an injury, the causative factors often are not readily discernible. In 50 per cent of the cases there was a history of trauma to the head, usually of a considerable force, although in some cases the injury was slight and did not produce unconsciousness immediately. Some patients recovered from the initial symptoms, and a latent period, of varying extent, intervened before the development of the syndrome leading to surgery. When this latent period lasted from one to fifteen years, the relation of the previous trauma was not always clear.

Table 2. *Etiologic Factors in All Cases.*

Factor	No. of Cases
Trauma	22
Hypertension	4
Arteriosclerosis	2
Syphilis (doubtful)	1
Embolus	1
Otorrhea, prolonged	1
Coryza	2
Vomiting	1
None found	10

In 25 per cent of the cases no etiologic factor could be found; in the remaining 25 per cent vascular disease was present only six times. Two cases followed shortly after an upper respiratory infection. A summary of the etiologic factors is given in Table 2. Figure 1 shows that most cases — 82 per cent — occurred in men and were distributed throughout all the age groups, although none were found in the first decade. The location of the lesion is given in Table 3.

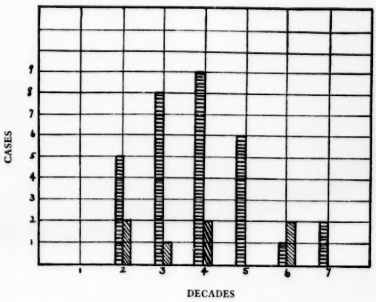

Figure 1. *Age and Sex Incidence (2 cases omitted). The horizontally lined blocks represent males; the cross-hatched ones, females.*

The post-traumatic hematomas are rather easily recognized, especially when the trauma produces symptoms that gradually progress to coma and when focal signs appear. Nevertheless, those that have a free interval and then a slow, progressive course are often mistaken for a neoplasm and in most cases cannot be differentiated by the most diligent investigations. The etiology of the so-called "spontaneous hematomas" is obscure, especially in those cases in which the onset is slow and the progress is intermittent over a long period of time.

TABLE 3. *Location of Hematoma in All Cases.*

LOCATION	NO. OF CASES
Frontal	8
Frontoparietal	10
Temporal	10
Temporoparietal	3
Temporo-occipital	2
Parietal	6
Parieto-occipital	1
Occipital	1

The mechanism of the fundamental pathologic process is obscure. Various authors have thought that simple fatty degeneration of the small arteries is an important factor in the development of spontaneous intracerebral hemorrhage in children. Bagley[6] believed that spontaneous hemorrhage, either meningeal or intracerebral, was often due to the rupture of an aneurysm caused by arteriosclerosis, syphilis, trauma, infection or congenital defects. Craig and Adson[8] have stated that the bleeding probably was due to venous rupture. Alexander and Putnam[13] also think that venous thrombosis is an important factor in the development of many intracerebral hemorrhages. Many other authors[14] have investigated intracerebral hemorrhage, but none have explained why some cases have a massive hemorrhage or an ordinary capsular stroke and why others result in hematoma formation.

The content of the hematoma varies according to the age of the lesion. In early cases there is almost unchanged blood or fresh clots, whereas the late lesions may be cystic and show, as Robinson[15] has stated, only gitter cells containing blood pigment adjacent to the capsule as evidence that the cyst originally was a hematoma. The development of a well-marked capsule, as described by Robinson and also by Douglas,[16] is unusual; complete cicatrization of the hematoma has never been recorded, although multilocular cyst formation may occur. Usually there is only a glial and connective-tissue reaction in the brain substance surrounding the extravasated blood. In some cases there is laminated clot, which suggests recurrent bleeding.

DIAGNOSIS AND TREATMENT

As already mentioned, the majority of the intracerebral hematomas come to operation with the diagnosis of brain neoplasm, although the early post-traumatic cases are usually recognized. The time that may elapse between the trauma and operation is extremely variable (Fig. 2); the earliest operation was done eight hours after the injury, whereas the latest operation, in Case 3 of the group reported in this paper, did not take place until fifteen years after the trauma. The most favorable cases for operation seem to be those in which the development of the syndrome of increased intracranial pressure is gradual and accompanied by signs of a lesion implicating the more accessible areas of the brain. In these patients, the motor fibers in the internal capsule are involved by pressure from a distance and the resulting paralysis is not complete. However, it is possible that a certain number of slowly increasing massive intracerebral hemorrhages might respond favorably to aspiration before rupture takes place; such a case was cited by de Lauwereyns[1] and is included in Table 1. It is interesting to mention that Craig and Lipscomb[17] have reported a successful operation in a case of intraventricular hemorrhage due to a hemangioma in the wall of the lateral ventricle. Puech, Rappoport and Brun[18] have described the removal of localized intraventricular hemorrhages. In some cases of intracerebral hematoma, single or repeated aspirations are sufficient for a cure; in others, incision of the cortex and evacuation of the fluid and clots are necessary. Encephalography or ventriculography may be required for accurate localization.

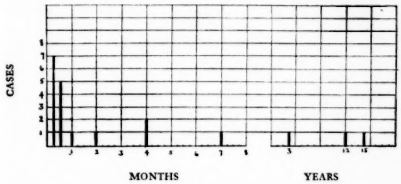

FIGURE 2. *Elapsed Time between Trauma and Surgery (2 cases omitted).*

PROGNOSIS

There were 9 deaths in the group of 41 cases in which operation was performed, a mortality of 22 per cent. Two deaths were due to pneumonia on the tenth and fourteenth days after operation, and 1 resulted from a known pre-existing *Streptococcus viridans* infection. If these

deaths were excluded, the surgical mortality would be 15 per cent.

Summary

Four cases of intracerebral hematoma are reported that were treated successfully by surgery. Thirty-seven other cases were found in the literature. Most of these cases responded well to surgical treatment.

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HYPOTHYROIDISM IN INFANTS AND CHILDREN*

With Reference to the Ultimate Prognosis Concerning Intelligence and to the Withdrawal of Thyroid Therapy as a Diagnostic Measure

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ALTHOUGH cretinism has for many years been known to result from deficiency of thyroid secretion, and although thyroid has had wide use in its treatment, an exact basis for a clear statement of the fate of treated cretins is still wanting. This is particularly true of eventual mental growth. The present study represents an attempt to secure more accurate information.

Lucas,[1] in 1927, presented the consensus when he said that treatment is usually followed by satisfactory physical results if begun early, although normal mentality is almost never attained; also, if the condition is recognized early, the continued administration of thyroid may produce a normal adult, but if treatment is delayed until the symptoms are so definite that the diagnosis is perfectly obvious, in most cases the child never gains actual normality.

Wieland[2] stated that results were less good in so-called "early infantile" or congenital athyreosis than in acquired myxedema of children or adults; he pointed to hopeful cases that were diagnosed and treated soon enough, but in patients untreated for years he noted a poor response to treatment, particularly in intellectual development.

Fordyce,[3] in 1933, after pointing out that the deficiency of thyroid may be of any degree, said that when careful treatment was begun in infancy and conscientiously continued, the ultimate prognosis was on the whole very good, although always uncertain. Some patients passed through childhood indistinguishable physically and mentally from normal children, and grew up into responsible citizens; others, however, responded only partially and became physically or mentally retarded, or both.

Holt and McIntosh,[4] in 1936, stated, "We have not seen normal mental development, even in cases in which treatment was begun during the first year of life."

Rolleston,[5] in 1934, emphasized that the earlier in life thyroid deficiency began, the less likely was well-marked benefit to result from thyroid therapy. Further, the earlier this treatment was started, the better were the prospects of success.

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†During the years 1933 to 1936, Dr. Goodkind made the observations included in this paper at the Harriet Lane Home, Baltimore, and the Massachusetts General Hospital. Dr. Goodkind died on September 3, 1937; he had collected the data, but had not recorded an interpretation of the results. The tabulation, the conclusions and the preparation of the paper were completed by Dr. Higgins.

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Observations have been made on 23 patients (13 from the Harriet Lane Home and 10 from the Children's Metabolism Clinic of the Massachusetts General Hospital) who had been under sustained treatment for thyroid deficiency — cretinism — for a period of five and a half to twenty-four years.

The purpose of this study was to assemble data bearing on the ultimate prognosis of this group of patients with regard to mental capacity, especially as correlated with the age at the time of diagnosis and beginning of treatment, with the maintenance dose of thyroid (degree of functional deficiency of the patients' own thyroid glands), and with the presence or absence of normal growth. The therapy of many patients was omitted for eight weeks; basal metabolism and blood cholesterol determinations were made before and four and eight weeks after the medication was discontinued.

In selecting the patients, availability for study was the main criterion.

The results are recorded in Table 1. Patients marked *"H"* were seen at the Harriet Lane Home, those marked *"M"* at the Massachusetts General Hospital.

The patients are listed in six groups according to their intelligence quotients, which were determined by Binet-Simon tests, fourteen years being regarded as the adult level. Thyroid therapy was being given at the time of the tests.

Physical growth is indicated by height, which is recorded as "normal" when it was normal for age and family size, and as "under normal," when it was definitely subnormal.

The maintenance dose of thyroid is that which the patient was receiving at the time this series of observations was begun. It is recorded as desiccated thyroid gland *U.S.P.* (Armour or Parke, Davis); where Burroughs and Wellcome thyroid had been taken, 1 grain is calculated as equivalent to ¼ grain *U.S.P.*

TABLE 1.

Case		Age	Sex	I.Q.	Age When Treatment Began	Height	Daily Dose of Thyroid	Course Without Thyroid: Basal Metabolic Rate 0 wk.	4 wk.	8 wk.	Blood-Cholesterol Level 0 wk.	4 wk.	8 wk.
		yr.			yr.		gr.	%	%	%	mg./100 cc.	mg./100 cc.	mg./100 cc.
1	*M*	25	M	112	1	Normal	1¼	+5	−25	−27*	152	220	310*
2	*H*	18	M	112	2 9/12	Normal	2	+25			175		
3	*H*	16	M	108	3	Under normal	1	−13	−14	−13	147	147	247
4	*M*	9	M	105	2/12	Normal	1	−1	−19	−33	175	356	480
5	*H*	17	F	95	2 6/12	Under normal	½	−8	−14		174	193	
6	*M*	16	M	90	7	Normal	1½	+4	−23	−25	154	210	417
7	*M*	14	F	87	10/12	Under normal	¾	−1	−18	−25	162	305	309
8	*H*	21	F	86	2	Normal	1	−5	−13		105	257	
9	*M*	17	F	85	2 6/12	Normal	1½	+5	−8	−25	178	305	329
10	*M*	8	F	78	1 7/12	Under normal	¾	+7	−4	−7	162	270	223
11	*H*	24	M	76	4	Normal	3	+17	+3	−20	110	183	
12	*H*	10	M	72	3	Under normal	1				114	208	
13	*H*	17½	F	69	3 6/12	Under normal	3	+19	−14		58	332	
14	*M*	12	F	67	6/12	Under normal	¾	+12	−13		191	312	
15	*H*	19	F	65	8/12	Under normal	1	−10	−17		185	428	
16	*M*	11	F	65	5 6/12	Under normal	1	+18	−14	−31	156	305	367
17	*H*	19	M	64	2	Normal	1	+17	+7†	+5‡	—	143†	160‡
18	*M*	17½	F	63	5 6/12	Normal	1½	§−7	−23	−21	§181	301	357
19	*H*	18	F	50	10/12	Normal	3		−2	−25	50	144	518
20	*H*	15	M	42	4/12	Under normal	1½	−16	−30		183		
21	*H*	19	M	42	4/12	Under normal	1½	+8	−12	−17	56	437	550
22	*M*	14	F	20	8/12	Under normal	1	+9	−11	−16	157	351	416
23	*H*	11	F	15	2 6/12	Normal	2	−2			148	375	848

*After being without thyroid for 6 mo.: basal metabolic rate, −27 per cent; blood-cholesterol level, 242 mg. per 100 cc.

†Six mo.

‡Seven mo.

§After being without thyroid for 12 wk.: basal metabolic rate, −29 per cent; blood-cholesterol level, 355 mg. per 100 cc. After 16 wk.: −41 per cent and 305 mg.

Basal-metabolism and blood-cholesterol determinations were made at the time the patient was receiving the usual dose of thyroid and four and eight weeks after treatment had been discontinued. The few cases in which the data cover longer periods are indicated by footnotes.

The age at which diagnosis was made and treatment begun is given in years. The diagnosis was made before the patient was one year old in 9 cases, and under two years in another case. Analysis of these histories indicates congenital thyroid deficiency (cretinism).

The diagnosis in the other 13 cases was made later, the patients being two years of age or over. One of these patients, Case 23, showed symptoms of hypothyroidism at six months of age; the diagnosis was not made and treatment was not begun until two years later (congenital hypothyroidism

with delayed treatment). Another patient (Case 6) was apparently normal—walking and saying words—at sixteen months of age; he had his first teeth at nine months. His symptoms began at four years of age, when growth stopped and lassitude and myxedema appeared; this patient had acquired myxedema and was not a congenital cretin.

The classification of the other eleven cases is more difficult. They are Cases 2, 3, 5, 8, 9, 11, 12, 13, 16, 17 and 18, and were recognized as cases of hypothyroidism relatively late. It is certain that the symptoms were not marked in the first year and a half of life; but there is information in the histories of each that makes one believe that the patients were then below par mentally and physically; as for instance delayed dentition or failure to stand, walk or say words at the normal age. An analysis shows that some congenital deficiency existed, but also that some thyroid function may have been present that later was lost.

Whether one is dealing at birth with true athyreosis, with partial thyroid deficiency or with normal thyroid function with loss of some or all function within the first two years of life, is always difficult to determine.

This differentiation of complete cretinism, partial cretinism, infantile myxedema and juvenile myxedema is hard to make because hypothyroidism has a gradual and insidious onset, because maternal hormone, absorbed by the child in utero, affords protection from symptoms for a considerable time, because minor amounts of hormone may be obtained from milk and food, because the patient himself cannot give a history pertinent to the diagnosis, and because wishful thinking on the part of many parents obscures deficiencies in their infants. Therefore, it has seemed best to group all the cases in one table.

Six patients showed a normal intelligence quotient, four being above 100. This does not agree with the usual impression that normal mentality in a cretin is never found. However, 6 patients were of low normal intelligence, and 11 were retarded. The mean mental level is marked by an intelligence quotient of 72.

Clinically, some cretins reach normal physical development under treatment, whereas others remain dwarfed to a greater or less degree. Of our group, 12 were definitely under normal height. The mean intelligence quotient of those of normal height was 85, and of the dwarfed group 68. Although the mental level tended to be higher in patients of normal height, in several cases of normal mentality the physical response to glandular therapy was subnormal.

Experience at the Children's Metabolism Clinic of the Massachusetts General Hospital has indicated that the daily dose of thyroid *U.S.P.* (Armour) necessary to maintain normal metabolic function in completely athyreotic children is ¼ gr. per year of life up to six years of age; 1½ gr. is sufficient for older children and adults.[6] In practice, however, the daily dose is based on the clinical reaction as well as on the basal metabolism of the individual patient; some patients do better with larger doses, and others, especially the mentally retarded, do not react well socially on the dose necessary for maintenance of normal basal metabolism, and should accordingly receive less.

Examination of the data from the patients in our study seems to confirm the general thesis that the 1½-gr. dose for athyreotic patients is sufficient to maintain normal metabolism, and also a normal blood-cholesterol level. Only Cases 18, 20 and possibly 23 indicated a slightly higher need for thyroid; on the other hand, Cases 2, 11, 13 and 19 were receiving larger doses than 1½ gr., but also had high metabolism or hypocholesterolemia or both.

Of the 6 patients with normal intelligence, 3 required full dosage of thyroid (Cases 1, 2 and 6), and 1 probably full dosage (Case 3), whereas 2 did not require full dosage for normal metabolism (Cases 4 and 5). In the group with low normal intelligence, full dosage was required in 2 (Cases 9 and 11), probably full dosage in 1 (Case 8), and less than normal dosage in 3 (Cases 7, 10 and 12). The respective figures for the retarded group were 7 (Cases 13, 15, 18, 19, 20, 21 and 23), 0, and 4 (Cases 14, 16, 17 and 22). Thus the percentages of complete athyreotic patients in each group were essentially the same: 66, 50 and 64.

The conclusion seems justified that the dosage of thyroid needed to obtain normal metabolism was not a factor in the ultimate mental capacity of the patient when under treatment.

Of the 11 cretins diagnosed and treated early, 6 received full dosages of thyroid and 5 did not require full dosage. Of the 12 cases diagnosed later, 6 required full dosage, 2 probably full dosage, and 4 only part dosage. The time of diagnosis and beginning of treatment did not determine the dosage needed later.

The age at which diagnosis was made and treatment started was also by no means the deciding factor in the ultimate mental capacity. In fact, the cases diagnosed as cretins and receiving first treatment early tended to be in the mentally retarded group; whereas only 2 cases among the patients with normal mentality were diagnosed before one year of age, there were 6 among the mentally retarded group. The diagnosis in Case 4 was made early because an older sibling had been a cretin.

Interpretation of these findings is difficult be-

cause we doubtless are dealing with different degrees of early thyroid function. Certainly mental retardation, if present, may lead to earlier recognition by parents and the physician that the child is abnormal.

Since the physical dwarfism, the maintenance dose of thyroid, and the age when treatment began are not clear-cut factors causing mental incapacity in hypothyroidism of children, the mental retardation may quite well have the same etiologic cause as the athyria in certain cases, and the athyria may not be the cause of the mental retardation. The athyria would thus be looked on as causing mental slowing and not mental incapacity.

It has been the practice at the Massachusetts General Hospital to photograph each untreated cretin; this is a valuable procedure, since the signs and symptoms of cretinism disappear within a few weeks after treatment with thyroid is begun; a later review of the case for diagnosis is thus made more satisfactory. It frequently happens that a patient has been diagnosed as hypothyroid elsewhere and placed on thyroid therapy; later, the question of whether the diagnosis was correct arises, and withdrawal of therapy is usually the only sure way to establish the diagnosis.

In 22 of our 23 patients, this was done; in 21, determinations of basal metabolism or blood cholesterol or both were made after four weeks and again after eight weeks, and in 2 cases also at longer intervals. In most of the patients, the laboratory tests as well as clinical observations had proved the diagnosis of hypothyroidism after four weeks, and in all after eight weeks. One patient (Case 17) was apparently no longer suffering from hypothyroidism at the time of the study; after seven months without thyroid therapy the basal metabolism and blood-cholesterol level were normal, although three years previously the metabolism had dropped from +10 to −21 per cent after fifty-six days' withdrawal of therapy. This patient offers an exception to the statement, "Once a cretin, always a cretin."

The blood-cholesterol level as an index of the

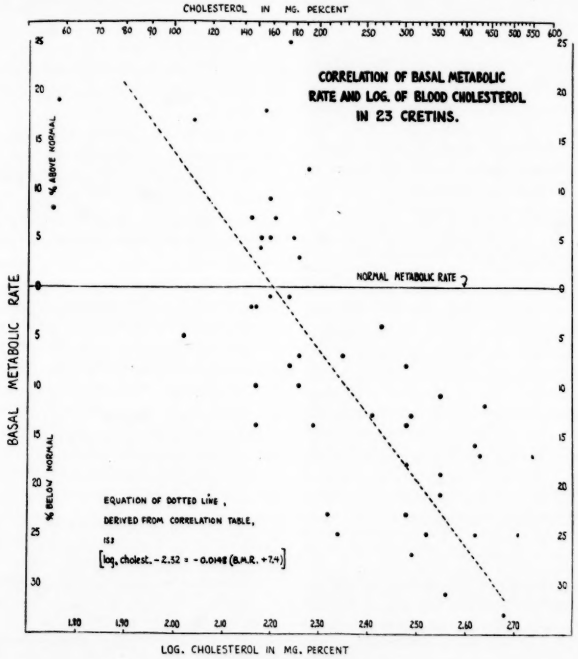
CHOLESTEROL IN MG. PERCENT
60 70 80 90 100 120 140 160 180 200 250 300 350 400 450 500 550 600
CORRELATION OF BASAL METABOLIC RATE AND LOG. OF BLOOD CHOLESTEROL IN 23 CRETINS.
% ABOVE NORMAL
NORMAL METABOLIC RATE
BASAL METABOLIC RATE
% BELOW NORMAL
EQUATION OF DOTTED LINE, DERIVED FROM CORRELATION TABLE, IS:
[log. cholest. − 2.52 = −0.0148 (B.M.R. +7.4)]
1.80 1.90 2.00 2.10 2.20 2.30 2.40 2.50 2.60 2.70
LOG. CHOLESTEROL IN MG. PERCENT

FIGURE 1.

state of thyroid sufficiency has been quite well established both for hyperthyroidism and hypothyroidism. Hurxthal[7] found that the hypercholesterolemia of hypothyroidism is marked and consistent and concluded that in the absence of a few other common causes, it indicated thyroid deficiency more specifically than the finding of a low basal metabolic rate.

Having at hand fifty-six parallel determinations of the blood-cholesterol level and the basal metabolism of cretins aged eight to twenty-five years, both when receiving and not receiving thyroid, we considered it desirable to try to correlate these findings. This has been done in Figure 1.

The correlation of the logarithm of the blood cholesterol value, in milligrams per cent, with the basal metabolic rate, in terms of percentage deviation from normal, shows that a significant relation exists and that the equation,

$$\text{Log. (cholesterol)} - 2.32 = -0.0148\ (\text{B.M.R.} + 7.4),$$

will allow the prediction of the cholesterol with an error of about 17 per cent, or .07 in terms of logarithms.*

Analysis of our data confirms the findings that cholesterol determinations of the blood serum or plasma are a good index of the degree of hypothyroidism and correlate well with the metabolic rate determinations. The method of choice in evaluating treatment apparently depends on the availability and ease of the two laboratory procedures. The low cholesterol findings before treatment in Cases 13 and 19 suggest that 3 gr. of thyroid was too big a dose; the findings in Cases 11 and 21 are similarly suggestive.

Summary

Observations were made on 23 hypothyroid patients under treatment from five and a half to twenty-four years, all but one, so far as can be ascertained, being not wholly normal during the first year of life, and therefore probably congenital cretins.

Six showed intelligence quotients between 90 and 112, 6 between 70 and 89, and 10 below 70.

Although the mean intelligence quotient was higher in the patients of normal physical growth than in the dwarfed, 2 of the dwarfed group had normal intelligence and many of normal size were mentally retarded.

The age of diagnosis and beginning of treatment was usually earlier in the ultimately mentally retarded cases than in those of normal intelligence.

The criterion that 1½ gr. of thyroid *U.S.P.* daily will raise to normal the basal metabolism of the athyreotic patient over six years of age was confirmed.

The degree of thyroid deficiency, as measured by the amount of thyroid necessary to maintain normal metabolism, was not proportional to the degree of mental retardation.

The cholesterol content in blood serum or plasma showed close correlation with the basal metabolic rate.

Since the ultimate mental capacity of the hypothyroid child under adequate treatment was not strictly related to physical growth, to delay in beginning treatment or to the dose of thyroid necessary for normal metabolism, the cerebral deficiency can probably be regarded as congenital and from the same cause as the thyroid damage.

Determinations of the basal metabolic rate and the blood-cholesterol level following the withdrawal of thyroid therapy are of diagnostic significance in the doubtful cases of treated cretinism.

*We are indebted to Professor E. B. Wilson, of the Harvard School of Public Health, for this statistical analysis.

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ACUTE LARYNGEAL OBSTRUCTION AS A COMPLICATION OF MEASLES

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ACUTE laryngeal obstruction is a rare but serious complication of measles. Very few textbooks on the subject of pediatrics and communicable diseases mention this sequela, and a perusal of the literature reveals that little consideration is given to it.

Morse,[1] Barnhill,[2] Coakley[3] and Scheppegrell[4] mention this complication in the discussion of measles, but they do so in a cursory manner, and say little or nothing concerning its management.

Homrighouse and McKee[5] cite a case of a twenty-one-month-old boy who developed obstructive laryngeal symptoms on the tenth day of measles. The boy was anesthetized for the purpose of bronchoscopy, but died suddenly while under anesthesia.

Oliver and Turner[6] described 3 cases of laryngeal obstruction that occurred during an epidemic of measles in Beirut, Syria, in 1933. Obstructive symptoms in all 3 cases developed during the height of the rash; all were treated by tracheotomy. Two of the children survived.

Neffson and Wishik[7] discuss this subject in their classic paper on acute infectious croup. Their findings are most interesting because they present the largest series of cases—35 patients. Statistically, the condition of acute laryngeal obstruction occurred in less than 1 per cent of the total number of cases of measles (3677) admitted to the Willard Parker Hospital from June, 1931, to June, 1934. Contrary to most opinions, acute laryngeal obstruction can occur at any stage of measles—in the pre-eruptive, eruptive or post-eruptive stage. Pathologically, these cases showed the edema to be located chiefly in the supraglottic area, and usually present to a marked degree. Laryngeal cultures showed *Staphylococcus aureus* or *Streptococcus haemolyticus* as the offending agent in about equal proportions. About 50 per cent of the cases went on to develop pneumonia as a further complication.

In the experience of the authors mentioned above, treatment by intubation was not the method of choice, for in their hands 6 of the 7 patients treated by intubation died.

It is obvious, of course, that, for the relief of laryngeal obstruction, intubation is a far better procedure than tracheotomy from the point of view of final result and comfort of the patient. If properly done and if the patient is carefully supervised while the tube is in the larynx, intubation causes fewer complications, is less devastating to the patient and esthetically is the procedure of choice.

The following 3 cases of acute laryngeal obstruction complicating measles have come to my attention in the last two years.

CASE REPORTS

CASE 1.† P. O. (No. 96619), a 2-year-old boy, sick for 4 days with measles, entered the South Department of the Boston City Hospital. For the few hours before entry he experienced rapid breathing, cyanosis and moderately deep suprasternal, substernal and intercostal retractions. The voice was hoarse, the breath sounds were somewhat diminished throughout, and there were many scattered moist rales in both lungs. The patient was placed in a croup tent and given steam inhalations, but his condition became progressively worse. He was laryngoscoped, a culture of the larynx was taken, and he was intubated by visual method that evening, a No. 1 tube being used. The culture showed a predominance of *Streptococcus haemolyticus*.

During the next 6 days he seemed comfortable with the tube in the larynx, but on the morning of the 7th day he coughed up the tube and his condition became immediately alarming. It was necessary to reintubate him within a few hours. This time a No. 2 was used. This was kept in place for 1 week. The patient improved markedly, and on the 7th day he was extubated by the visual method; he was discharged 2 days later in good physical condition, except for slight hoarseness.

CASE 2.‡ W. O'C., a 4-year-old boy, was admitted to the Belmont Hospital, Worcester, Massachusetts, after a hurried 25-mile trip over the highway, in a precarious condition. He was markedly dyspneic and presented marked substernal retractions. There was a fading erythematous maculopapular rash, with marked injection of the conjunctivas, injection of the posterior pharynx and enlarged, boggy tonsils. Harsh breath sounds were heard in the upper part of the chest only. The larynx was not visualized, but on indirect intubation marked edema of the epiglottis was noted. A culture of the nose and throat showed *Staphylococcus aureus*. No laryngeal culture was attempted.

The patient was intubed immediately after admission by the indirect method, without apparent relief. He was therefore extubated, but the retractions became so severe that he was almost immediately reintubated, this time with good effect. He spontaneously extubated during the night of admission, and was again reintubed. During the next 4 days the patient's condition continued to improve. On the 5th day he again spontaneously extubed and had to be

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†By permission of Dr. Edwin H. Place, chief physician of the South Department, Boston City Hospital.

‡By permission of Dr. Elizabeth Bishop, resident physician, Belmont Hospital.

reintubed once more. On the following day, he again coughed up the tube, but his condition seemed so improved that reintubation was not considered necessary. Convalescence from then on was uneventful, and he was discharged on the 14th day with no abnormal physical findings other than a slight huskiness of the voice.

CASE 3. R. O'C., a 4-year-old boy and a brother of W. O'C. (Case 2), entered the isolation unit of the Burbank Hospital on the 2nd day of a measles rash, because of a sudden and progressive respiratory difficulty, a moderate degree of cyanosis and a marked hoarseness of voice. He was extremely restless, and breathing involved marked infrasternal and suprasternal retractions. He was placed in a croup tent and given steam inhalations, but the degree of obstructive symptoms became more marked. A throat culture taken at this time revealed rare gram-positive diplococci, occasional *Staph. aureus* and a short-chained streptococcus; no *Corynebacterium diphtheriae* were seen.

Laryngoscopy showed considerable swelling of the subglottic and supraglottic areas. A No. 3 tube was inserted into the larynx, with prompt relief of symptoms. One hour later in an attack of spasmodic coughing the tube came out, and was reinserted by the visual method. He was again relieved of obstructive symptoms and went to sleep. About 6 hours later he coughed up the tube, and this time a No. 4 tube was inserted. This tube fitted rather snugly. He kept this tube in and improved rapidly from that time on. On the 3rd day his temperature fell to normal, and the patient was extubated by the visual method. The symptoms did not return, and he was discharged on the 5th day in good physical condition.

SUMMARY

This paper calls attention to the infrequent but serious complication of acute laryngeal obstruction in measles. Three cases are presented that were treated by intubation. Characteristic of this type of management is the necessity for careful nursing supervision and frequent reintubation, but this is compensated for by the infrequent occurrence of complications and by the freedom from the danger of repeated blocking, which is always present when a tracheotomy tube is used. In addition, there is no scarring of the neck, a condition of benefit to the patient in later life.

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CLINICAL NOTE

A NOTE ON PAIN AND ITS REFERENCE IN CASES OF RENAL INFARCTION

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STIMULATED by a history of unusual reference of pain to the testicle as the result of renal infarction in Case 26231[1] of the "Case Records of the Massachusetts General Hospital," we have reviewed the symptomatology in one of the larger reported series of cases of infarct of the kidney proved at post-mortem examination, and in cases encountered at the Massachusetts General Hospital in the last seven years. In 1933, Barney and Mintz[2] reported an analysis of 143 cases of renal infarct from the autopsy records of the Massachusetts General Hospital. Of this series, 117, or 83 per cent, were on the medical wards. Almost all the patients on the medical services were found to have acute or chronic heart disease. Sixty-eight per cent of the cases were afebrile. Nausea and vomiting were rare, being noted in only a little over 8 per cent. In 88 cases, or 65 per cent, there was no pain or tenderness at any time. Among the cases with pain and tenderness, none were associated with costovertebral tenderness, which has so often been associated with renal disease. There was no mention of the symptom of typical renal colic in any case.

Among 75 cases of renal infarction that came to autopsy at the Massachusetts General Hospital during the seven years from January 1, 1933, to January 1, 1940, 20 patients gave histories of recent or fairly recent abdominal pain. However, most of the cases were eliminated because of the location of the pain and because of its association with other complicating abdominal conditions, such as cholecystitis, cholelithiasis, dissecting aneurysms of the abdominal aorta, renal carcinoma, nephrolithiasis and mesenteric thrombosis. There remained 3 patients with histories typical of renal colic — severe pain in the sides of the abdomen or flanks, costovertebral tenderness, nausea and vomiting — in whom no other intra-abdominal condition existed to account for the symptoms. In 2 of these cases, the pain radiated down to the lower quadrants of the abdomen, but in no case was there radiation of the pain to the genitalia.

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Other rare cases of renal colic and radiation of pain to the genitalia in renal infarction have been encountered, as noted by Aschner,[3] who recorded 2 cases, by Falci,[4] who cited 1 case (among 22 of renal infarction collected from the literature, in most of which there was flank or lumbar pain, with reference to the thigh in a few and with vomiting in a few), and by Loeb,[5] who, in a discussion of diseases of the kidney, remarked that in renal infarction it was possible to have a clinical picture identical with that of renal colic.

It has been suggested by Ehrström[6] that the pain in renal infarction is due to swelling of the kidney and consequent stretching of the capsule.

The pathogenesis of the striking renal colic in Case 26231, with unusual radiation of pain to the testicle, such as is characteristic of renal and ureteral calculus, can be adequately explained as the result of referred symptoms from the renal involvement alone, without the need of incriminating ureteral or bladder lesions. It is unlikely that a blood clot passing through the ureter would have caused the pain, because the pain came at once, before the blood clot might have formed, and because there was very little actual blood in the urine.

It has been mentioned at times that the clinical picture of renal infarct can so simulate that of true renal colic that in rare cases such patients are operated on for the removal of the supposed stone. However, we were unable to find any such case in the autopsy and surgical pathological files of this hospital, and conversations with members of the urological staff failed to reveal any such case.

Thus, in renal infarction, pain is oftener absent than present, renal colic is very uncommon and radiation of pain to the genitalia is exceedingly rare.

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MEDICAL PROGRESS

HEMATOLOGY*

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Infectious Mononucleosis

SINCE cases formerly diagnosed as "grippe," influenza, septic sore throat, mesenteric adenitis, appendicitis, continued fever and so forth are being recognized as examples of infectious mononucleosis, the importance of this disease in general practice is gradually becoming more and more evident. That the disorder frequently, if not usually, goes unrecognized is by now a truism. If the practitioner were to examine carefully for enlarged lymph nodes and spleen in every case of fever, the percentage of recognized cases would be greatly increased. Too often, it seems, the throat, heart, lungs and abdomen are examined with very little attention to possible lymphadenopathy. If, furthermore, blood smears were made routinely, the disease would be recognized far more frequently. The blood picture is so characteristic, once it is known and recognized, that it permits ready diagnosis. There is lymphocytosis (not monocytosis), the lymphocytes being of all possible sizes, shapes and staining characteristics. Great variability in the type of lymphocyte is the outstanding feature — quite the reverse of acute leukemia, in which a "monotonous" blood picture with one type of lymphocyte, usually the lymphoblast, predominates. There is furthermore no anemia, and hardly ever any reduction in blood platelets — again quite in contrast to acute leukemia, in which rapidly progressive anemia and thrombocytopenia are the rule. The introduction of the heterophil agglutination test has been of material aid in further defining these cases, which usually give a positive agglutination reaction with sheep's red blood cells.

There is almost no limit to the bizarre manifestations of the disease. As in all generalized conditions (polycythemia, metabolic disorders and so forth) peculiar localizations occasionally crop up. Jaundice, which looks typically like the catarrhal type, may be the presenting symptom. A case of this type, associated with a positive Wasser-

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mann reaction, is reported by Fowler and Tidrick.[1] As these authors point out, "it is not improbable that many cases diagnosed as catarrhal jaundice have actually been infectious mononucleosis." Positive serologic tests for syphilis not infrequently occur concurrently with the positive heterophil reaction. Bernstein,[2] who gives a comprehensive review of the disease, found a transiently positive Wassermann reaction lasting for two or three weeks in 8 of 44 cases. On the other hand, Davidsohn,[3] of Chicago, who has been responsible for some of the outstanding work with the heterophil reaction, has failed to find one case with positive serologic tests for syphilis in his carefully studied series. At any rate, changes in the serum may cause agglutination of sheep's red cells and positive Wassermann, Kahn and Hinton reactions. These changes are apparently not the result of the same serologic abnormality, but their mechanism is at present unknown.

Bernstein, in his review, cites such symptoms as edema of the eyelids, skin eruptions, and central-nervous-system manifestations, which are occasionally present. Templeton and Sutherland[4] point out the frequency of an exanthem in the disease — 17 of 91 cases. In 12 cases, the rash was practically indistinguishable from that of German measles. In this connection, it should be noted that the latter disease is associated with well-marked lymphadenopathy and not infrequently with an abnormal lymphocytic reaction in the blood; one wonders whether they might be related.

The etiology of the disease and the manner of its spread remain obscure. Epidemics are occasionally seen, but even in these, the type of spread has not been worked out. The pathology of the disorder has naturally not been extensively studied because of the absence of autopsied material. However, biopsied lymph nodes have resulted in an understanding of the fundamental nature of the lymphocytic proliferation. Gall and Stout,[5] on the basis of ten biopsied lymph nodes, claim that there is a specific pathologic picture. This is characterized by marked proliferative activity of the pulp, extensive but focal proliferative activity of clasmatocytes and the appearance of large numbers of specific so-called "infectious mononucleosis cells." These are large lymphocytes with abundant basophilic cytoplasm, which with phloxin and methylene blue stains have a filmy-blue quality of the cytoplasm.

The prognosis is always good. There is no specific therapy for the disease, which indeed usually requires only symptomatic treatment. The sulfonamide drugs are of no value unless there is a secondary infection with streptococci or pneumococci. Occasionally there is a rather marked, associated Vincent's infection, which may cause a severe cervical adenitis. If this is present, an injection of 0.3 gm. of neoarsphenamine intravenously may be of great benefit.

Reactions of the Blood to Drugs

The reactions of the blood cells to the sulfonamide group of drugs continue to be the subject of much comment. These drugs have an effect on hemoglobin that is usually slow but may occasionally be rapid (acute hemolytic anemia). In the slow type of response, methemoglobin and sulfhemoglobin, which are inactive pigments, are slowly formed, and are probably responsible, at least in part, for the cyanosis commonly noted. Earlier conflicting results regarding the presence or absence of these pigments have been resolved by greater accuracy of methods. Smith,[6] experimenting with white rats, found that sulfanilamide given orally for a month caused small but significant amounts of methemoglobin and somewhat larger amounts of sulfhemoglobin. There was a definite reduction in hemoglobin. These results are borne out in human observations by Harris and Michel.[7] The degree of methemoglobinemia was proportional to the sulfanilamide concentration. Vigness, Watson and Spink[8] found that the cyanosis of sulfanilamide therapy could be explained by the presence of methemoglobin, rarely sulfhemoglobin, and that methylene blue abolished the cyanosis as well as the abnormality of hemoglobin pigment. Erf and MacLeod[9] noted an increase in fecal urobilinogen output (increased blood breakdown) in cases of pneumonia treated with sulfapyridine. Three of 8 cases so treated developed a definite hemolytic anemia. Paul and Limarzi[10] found that the bone marrow became more hyperplastic after sulfanilamide administration, again indicating a hemolytic effect. Spence and Roberts[11] report a case of extreme leukocytosis and acute hemolytic anemia with sulfanilamide administration. They point out that leukocytosis may be an early hidden manifestation of a hemolytic process associated with administration of the drug.

The subject of acetanilide poisoning has received scant attention in comparison with that of the toxic reactions of the sulfonamide drugs. However, Meulengracht and his collaborators[12] have very properly revived interest in the matter, especially since drugs such as Bromo-Seltzer are so commonly used in this country. As with sulfanilamide, acetanilide rapidly produces cyanosis, which for years has been thought to be due to methemoglobin or sulfhemoglobin. These authors found that the cyanosis was caused by the decomposition of acetanilide to dark-colored derivatives of

para-amidophenol. Since continuous use of the drug is followed by "a peculiar and gray addiction" with persistent fatigue and headache, the authors recommend that prescriptions for the drug should not be refilled. In this country more stringent regulations might well be made.

Iron-Deficiency Anemia (Hypochromic Anemia)

Chronic iron-deficiency anemia is usually the end-result of a group of etiologic factors: a diet inadequate in iron, achlorhydria, malabsorption of iron-containing material from the bowel, hemorrhage (menorrhagia and hemorrhoids), multiple pregnancies and so forth. One factor alone is rarely at fault in these cases, although achlorhydria may be the crux of the problem. Thus cases with such abnormalities as impaired dietary and menorrhagia might develop very little anemia unless the gastric juice were also affected.

Iron-deficiency anemia in children is discussed by Abbott and Ahmann,[13] who studied a group of 883 rural school children in Florida. Half of them were anemic (below 70 per cent hemoglobin, Dare), and a hemoglobin between 70 and 85 per cent was found in nearly one third. A number of children had been born of anemic mothers and had probably been anemic to some extent for the greater part of their lives. Pallor, general muscular weakness, lassitude and a faint systolic murmur were commonly present when the hemoglobin level was below 50 per cent. As etiologic factors are listed poverty, food high in carbohydrate, hookworm infestation and various gastrointestinal disturbances. It is also possible that certain infants born in families with either pernicious anemia or chronic hypochromic anemia may have a constitutionally defective gastric mucosa, which might result in failure adequately to digest organic iron-containing foods.

By the use of radioactive (so-called "tagged") iron, Hahn and his co-workers[14] at the University of Rochester have been actively engaged in the study of iron metabolism. In animals, it is possible to study the labeled iron from the time it enters the circulation until it is excreted. Its incorporation in the hemoglobin molecule has also been studied.[15] In the dog with chronic iron deficiency, iron is rapidly taken up in the red blood cells, and the body cells are apparently avid for it, whereas the normal animal to a great extent rejects iron.

In the patient who has had a hemorrhage, as from a peptic ulcer, it has long been debated whether added iron was of value. Lyons and Brenner[16] contribute to this discussion by an analysis of 237 cases of bleeding peptic ulcer. The rate of erythropoiesis following hemorrhage appeared strictly dependent on the degree of anemia, and was "fully as good as that reported for patients treated with a liberal, 'puréed diet' and iron." Transfusion itself appeared to have no effect on the rate of red-cell production.

In pregnancy, the incidence of anemia is quite high, amounting, Bethell, Gardiner and MacKinnon[17] state, to 54 per cent of 158 cases studied. The majority of these cases were of the iron-deficiency type. Since normal gestation places no great demand on maternal iron stores, the anemia was due mostly to other factors: low iron reserves, restricted utilization of reserve iron, impaired absorption of iron during gestation and low dietary intake of iron. It should be noted that poverty and an inadequate intake of food iron frequently go together, since the foods containing large amounts of iron are for the most part the most expensive (meat, liver, green vegetables and eggs). If inorganic ferrous preparations are given in cases of hypochromic anemia, there is an excellent response; the routine use of iron during pregnancy is thus a justifiable procedure.

In males, chronic hypochromic anemia is almost always due to persistent bleeding, particularly from the gastrointestinal tract. Given a case of apparently idiopathic hypochromic anemia in a male, the stools should be searched for occult blood, and gastrointestinal studies should be instituted. Not infrequently, herniation of the stomach is discovered. A number of such cases have been reported in recent years. Two have recently been reported by Dyke and Dyas.[18] In the second case, occult blood in the feces was present, although the test was negative in the first case. A negative finding for occult blood does not necessarily rule out the possibility that the anemia is associated with the hernia, since persistent bleeding in the past may well have taken place.

Recently, the possibility that some types of vitamin deficiency might be linked with hypochromic, microcytic anemia has been discussed. Thus, in dogs, a deficiency in the "rat antidermatitis principle" — vitamin B_6 or pyridoxin — has been shown by Fouts, Helmer and Lepkovsky[19] to result in hypochromic anemia, responding to pyridoxin administration. This has been confirmed by Borson and Mettier.[20] Whether these experimental observations have any relation to the hypochromic anemia of human beings is questionable.

Chlorosis which is usually considered as practically extinct, is probably far commoner than is generally appreciated. It is likely that many diagnoses of chlorosis prior to 1900 were made without benefit of careful laboratory examinations, and it is therefore possible that many cases of such con-

ditions as pulmonary tuberculosis, chronic hemorrhage and even neurasthenia were diagnosed as chlorosis. In taking histories in adult women with chronic iron-deficiency states associated with achlorhydria, it is noteworthy that the great majority have been "anemic for years" or "anemic since childhood" or were "treated with iron twenty years ago." In all probability, many of the cases of chronic idiopathic or primary hypochromic anemia of late adult life have been examples of "chlorosis" in youth. The central feature of both these disorders is probably the histamine achlorhydria, which may indeed be indicative of a constitutional gastric atrophy. It is possible that this abnormality may lead to certain cases of so-called "nutritional anemia" in infancy, to chlorosis in puberty, and to primary or idiopathic hypochromic anemia of late adult life. Certain cases may furthermore develop pernicious anemia as a late manifestation. The marked reduction in hemoglobin that ensues with chronic iron deficiency results in a disappearance of the normal healthy red color from the skin, with the result that the basic yellowish color of the skin becomes quite obvious. Owing to a common tendency in medicine to exaggerate colors, the yellowish coloration has been termed "green," possibly because greenish overtones may be seen by the more artistic observers. Thus, the so-called "green-sickness" or chlorosis is in all probability simply a chronic iron-deficiency state of young people, usually young women, and usually with an atrophied gastric mucosa. In my series, and in that of Olef,[21] complete histamine achlorhydria was usually present. Response to inorganic iron is rapid, but relapses occur when the medication is discontinued, so that a maintenance dose is recommended.

Pernicious Anemia

Pernicious anemia is a deficiency disease. As such, it may result from an inadequate diet, a lack of digestion of protein by an atrophied gastric mucosa, which fails to produce "intrinsic factor," malabsorption by the bowel, or hepatic disease (inadequate storage), or in pregnancy it may follow the loss of liver-extract substance to the fetus. More recently, the possibility of lack of utilization of liver-extract factor by the body (so-called "achrestic anemia") has been postulated. It should be noted that in a given case, a number of etiologic factors may operate together. Thus, both the diet and the intrinsic factor may be grossly deficient; if only one were deficient, the patient might not develop the deficiency state. Multiple factors are thus important, and it should also be noted that the resulting changes in the body are also multiple. Pernicious anemia is not only an anemia; it is a generalized disturbance — a starvation of the body for liver-extract substance with the result that graying of the hair, glossitis, gastrointestinal manifestations and central-nervous-system disturbances result. The anemia is simply one aspect of the deficiency, resulting specifically from lack of liver-extract substance by the bone-marrow cells.

The constitutional nature of pernicious anemia is discussed in an article by Schemm,[22] in which 5 authenticated cases in the same generation of one family were studied. In addition, 2 cases in each of five families were observed. It is probable that all the hereditary cases are based on an inherited gastric (or gastrointestinal) mucosal atrophy with resultant diminution or even complete lack of intrinsic factor. Schindler, Kirsner and Palmer[23] discuss gastroscopic observations in the disease. Histologically, atrophic gastritis is chiefly characterized by extreme thinness of the gastric mucosa due to disappearance of the gastric glands. Schindler and his co-workers believe that the various changes are the end result of chronic inflammation, although most observers believe they are degenerative. A certain parallelism between changes in the tongue, the mucosa of the stomach and the spinal cord is usually present, although occasionally the gastric mucosa may be atrophied without changes of these organs.

Achrestic (lack of utilization) anemia has been described for the third time by Israëls and Wilkinson.[24] In their first papers, these cases of apparently typical pernicious anemia presented two unusual features: free hydrochloric acid in the gastric juice and failure to respond to liver-extract therapy. Because potent liver-extract principle was present in the livers of some of these autopsied patients, it was postulated that this material could not be utilized by the body. In the most recent paper, the authors' concepts have apparently undergone some modification, for of the 6 cases reported the only abnormality was the presence of free hydrochloric acid in the gastric juice. A definite response, perhaps somewhat slower than usual, occurred in all cases following the use of liver or gastric extracts. The matter of intrinsic factor in the gastric juice was not studied, although it appears (according to Castle's well-known experiments) that this is of greater fundamental importance than the presence of free hydrochloric acid. I recently observed a case similar to those reported by Israëls and Wilkinson, since the two uncommon features noted by them were present, in addition to the ordinary characteristics of pernicious anemia. Only when large doses of Ventriculin were given did the patient begin rapidly to improve.

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Sprue is probably another subtype of the larger pernicious-anemia syndrome. Castle and his co-workers[25] considered that the two diseases were identical, and it cannot be doubted that histologically and hematologically they often cannot be differentiated. Rodriguez-Molina[26] found that although the bone-marrow and hematologic aspects of sprue were identical with pernicious anemia, other features served for differentiation. Thus extremely bulky stools rich in fat, a low blood calcium, an increased sugar tolerance and a low rather than a high fecal urobilinogen output are characteristic of sprue and not of pernicious anemia. It is probable, however, that these are special symptoms perhaps representing, as stated above, a subtype of the larger syndrome. The matter of the fecal urobilinogen output is receiving increasing attention. It is the most sensitive method for determining the degree of blood destruction. In pernicious anemia, an increased output in the feces is always present. In sprue, as pointed out by Koller,[27] the output, as measured in 3 cases, was less than normal.

The duration of the remission in pernicious anemia has recently been studied by Strauss and Pohle.[28] The following conclusions are drawn: patients with pernicious anemia who require relatively little liver extract to maintain a normal blood level may relapse in as short a time as two months after liver therapy is omitted; the majority of patients with pernicious anemia cannot be satisfactorily treated by the use of massive doses of liver extract given at intervals of several months; and the optimum interval between injections for most patients is from one to four weeks. Another paper by the same group[29] dealing with therapy discussed combined degeneration of the spinal cord, with the results of seven years' experience with parenteral liver therapy. It was found that the neural lesions could be arrested in every case. If adequately treated, no case of pernicious anemia developed new neurologic disturbances. Adequate therapy should maintain the blood at a red-cell level of 4,500,000 or over, the color index at 1.0 or below and the mean corpuscular volume at 100 cu. microns or below; there must be no symptoms of any nature (glossitis, indigestion and so forth) attributable to pernicious anemia; and if there is recurrence of paresthesias or other subjective disturbances, the dose of liver extract must be doubled. Each patient's dosage is an individual matter. The material used by Strauss and his co-workers was a very dilute liver extract (1 unit per cubic centimeter), usually given in 10-cc. amounts weekly, although some patients required the material three times weekly. In my experience, the highly concentrated extracts are as effective as the dilute extracts, perhaps more so, in treating the neurologic lesions, and they are much preferred by the patient.

Hemolytic Anemias

Interest in this group of cases, which is characterized by increased blood destruction, has developed considerably in the last few years. The hemolytic anemias have been classified as follows[30]:

A. Congenital hemolytic icterus (anemia)
   1. Chronic, with or without crisis
   2. Subacute
   3. Acute (crisis)

B. Acquired hemolytic icterus (anemia)
   1. Secondary to known cause (infectious, chemical, "toxic," pregnancy and so forth)
   2. Symptomatic, in association with certain, usually malignant diseases, as lymphatic leukemia, Hodgkin's disease, carcinomatosis
   3. Of unknown cause, with or without hemolysins in the serum
      a. Chronic, with or without crisis
      b. Subacute
      c. Acute
      d. Acute fulminating, often with hemoglobinuria

This classification attempts to restore the former well-known grouping of congenital and acquired types, especially since there appears to be an unfortunate tendency to deny the existence of the acquired type.

Spherocytosis. The conception of the spherocyte is important in considering the hemolytic syndromes. About twenty years ago, Naegeli[31] pointed out that the red cells in congenital hemolytic jaundice tended on the whole to be smaller, rounder and thicker than normal, and he designated them "spherocytes." He believed that the disorder represented an abnormal production of cells in a faulty bone marrow, and that the spherocyte was the pathognomonic cell of the hereditary disease. This statement was universally accepted. In recent years, Haden[32] and others found that there was a direct correlation between the degree of thickness of the erythrocyte and its fragility to hypotonic solutions of sodium chloride. More recently, Dameshek and Schwartz[33] found hemolysins in the serum of 2 cases of acutely developing hemolytic anemia, in one of which marked spherocytosis was present. As the patient recovered after splenectomy, the hemolysin was no longer present, the spherocytosis gradually diminished and disappeared, and the saline fragility became nor-

mal. It was reasoned that perhaps the hemolysin and the spherocytosis were related. A hemolytic serum was therefore produced, which, when injected in guinea pigs, resulted in acute or subacute hemolytic anemia, spherocytosis, increased fragility and reticulocytosis. The degree of spherocytosis and anemia varied directly with the amount of hemolytic serum injected. Except for hyperplasia, the bone marrow was normal. These observations have recently been confirmed by Tigertt and Duncan[34] in dogs. Thus for the first time it was shown that spherocytosis could be produced without postulating an abnormal bone marrow. Spherocytosis in these experiments was shown to be the end-result of the activity of hemolysin, and the possibility was broached that a spherocyte represented a red cell that had already been damaged by a hemolytic agent. It seems likely that the spherocyte is the forerunner of complete hemolysis. It can be produced by immune hemolytic serums, by various chemicals, such as sulfanilamide, by hypotonic salt solutions and, in fact, by many agents that damage the red cell by various means. Although spherocytes of various conditions are morphologically indistinguishable, they may be quite different from the chemical or physical standpoints.

Mechanism. Although the presence of hemolysins may be the basis of many of the hemolytic syndromes, including acute hemolytic anemia and paroxysmal (cold) hemoglobinuria, Ham and Castle[35] have recently stressed the importance of intravascular stasis as a prime cause of increased blood destruction. They point out that the spleen is primarily a stasis organ, and that splenectomy is beneficial because the abnormal spherocytes are no longer subject to the hemolyzing effects of continued stasis in the spleen. They claim that increased agglutination (rather than hemolysis) is at the bottom of the experimental results of Dameshek and Schwartz, and show that a so-called "pure agglutinin" (concanavalin A) produces hemolytic anemia in animals. They point out many clinical applications of the so-called "erythrostasis theory." Although the conclusions of Ham and Castle are in certain respects probably correct (agglutinative hemolytic transfusion reactions, autoagglutinins and so forth), they fail to explain the lack of increased hemolysis in polycythemia — in which stasis is extreme — and in thrombosis of the splenic vein. That various hemolytic agents, free of any agglutinating reaction whatever, can cause hemolytic anemia is also not explained by this theory.

The relation of the spleen to increased hemolysis is still quite obscure. Ham and Castle postulate for the spleen a simple physical or passive function; they state that the condition of blood incubating in a test tube is in many respects identical with that in the splenic sinusoids. There is a possibility, however, that the spleen participates more "actively," perhaps through obscure cellular mechanisms. After all, the spleen is somewhat more than a test tube. The dramatic effects of splenectomy in many cases of hemolytic anemia are much in favor of this idea, especially in acquired cases when there is frequently a complete reversion of the blood picture to normal. Thus the theory of so-called "hypersplenism" or of hyperactivity of the entire reticuloendothelial system must be considered, at least in some cases.

In summary, it is likely that various mechanisms are responsible for the development of hemolytic processes. Haden,[36] in an admirable review of hemolytic anemia, states that the factors in increased hemolysis may be summarized as follows:

I. Increased hemolysis of normal cells damaged by foreign agents
   a. Chemicals
   b. Parasites
   c. Bacterial toxins
   d. Amboceptor and complement reactions (including hemolysins and agglutinins)

II. Increased activity of the spleen

The subject of pathogenesis is still in the process of elucidation, and the final word has certainly not been said.

Clinical studies. Farrar, Burnett and Steigman[37] found a hemolysin in a case of acute hemolytic anemia that was cured by splenectomy, thus confirming our own observations. Another case of acute hemolytic anemia, with spherocytosis and recovery after splenectomy, is reported by Mandelbaum.[38] This case is of interest in that it occurred in a seventy-five-year-old person. It also illustrates to what length writers will go to avoid the designation of acquired hemolytic jaundice. Since spherocytosis was present, a congenital hemolytic process was assumed, even though the patient was seventy-five years old, had no familial history, and had never previously been known to have either splenomegaly, anemia or jaundice. It should be continually stressed that spherocytosis is by no means pathognomonic of the congenital type. In a study of a case of typical hereditary hemolytic jaundice, Waugh and Lamontagne[39] make some interesting observations on the types of bilirubin present and on the hypotonic fragility of the erythrocytes. These observations are both carried out by utilizing the photoelectric colorimeter of Evelyn adapted to bilirubin and fragility measurements. Even in hemolytic icterus, a small amount of so-

called "direct" bilirubin was found. The hypotonic fragility, as determined with the photoelectric colorimeter, can be ascertained very accurately and shows very small degrees of hemolysis. With this technic Waugh and Lamontagne demonstrated that before splenectomy a few extremely fragile erythrocytes are present, disappearing after operation.

Careful and well-conceived studies of a rare type of hemolytic syndrome — "paroxysmal nocturnal hemoglobinuria" — have been made by Ham[40] and by Ham and Dingle.[41] Although the fundamental abnormality was found to reside in the red blood cells, a thermolabile factor essential for hemolysis and found in serum (complement) was also essential. The hemoglobinemia and hemoglobinuria were associated with sleep, and it is suggested that during sleep there is an increased intravascular hemolysis associated with increased acidity of the blood, especially of regions of the blood subject to stasis, such as the spleen. Further detailed studies bearing on the immunologic situations involved are described by Ham and Dingle.

A review of the cases of acute hemolytic anemia (acquired hemolytic icterus, acute type) has recently been made.[30] Many of these have been miscalled "Lederer's anemia," identical cases having been described many years ago by Widal and his collaborators and by Chauffard (1907–1914). These cases are characterized by acute or subacute onset, rapidly progressive anemia, jaundice without bile in the urine, an increased output of urobilinogen in urine and feces, and a variable blood picture. The concept that these cases are benign and respond to one or two transfusions has become prevalent; the reverse is, however, frequently true. In a number of cases, when several transfusions have been given and the patient has failed to respond, the possible dramatic results of splenectomy have unfortunately been ignored. To be sure, not all patients recover following splenectomy, which indeed is a serious procedure in this age group (usually from forty to sixty-five). My routine at the present time is to give one to three transfusions; if no definite therapeutic effect takes place, splenectomy is performed without further ado. If this procedure is postponed, the patient may develop new hemolysins or agglutinins, have severe transfusion reactions, and succumb to a final "last-ditch" operation.

Cooley's erythroblastic anemia. This disease is receiving increasing attention, and is found chiefly in children of Greek and Italian parentage, being characterized by hemolytic anemia, the presence of large numbers of nucleated red cells and bone changes. The latter are apparently due to marked hyperplasia of the bone marrow with expansion of the marrow cavities. Both Smith[42] and I[43] have described a new abnormality of the red cells in this disorder, namely, the "target cell." This erythrocyte, the antithesis of the thick spherocyte, is very thin, having the appearance of a bull's eye or target in stained smears, and is unusually resistant to hypotonic salt solutions. It may well be the inherited factor in Cooley's anemia. "Target-cell" anemia[43] is characterized by bone changes like those of Cooley's anemia, increased blood destruction, and the presence of many target cells with increased resistance to hypotonic salt solution. These cases are important in that they probably represent mild cases of Cooley's anemia, and the patients may reach adulthood and result in the propagation of the more outspoken disorder of Cooley's anemia. Under the title, "A Familial Hemopoietic Disorder in Italian Adolescents and Adults Resembling Mediterranean Disease (Thalassemia)," Wintrobe and his co-workers[44] describe a number of such cases. The name "target cell" was applied by Barrett.[45] This interesting cell is seen following splenectomy, in certain hepatic diseases, in Cooley's anemia and in sickle-cell anemia.

Leukoerythroblastic Anemia

In recent years, interest has developed in a condition characterized clinically by marked splenomegaly, slowly progressive anemia of the normocytic type, leukocytosis with the presence of myelocytes, metamyelocytes and a variable number of nucleated red cells, and irregular bone changes, as demonstrated by x-ray study. Histologically, a fibrotic bone marrow is usually found in association with myeloid transformation of the spleen (ectopic bone-marrow activity). The condition has been variously described as leukoerythroblastic anemia (Vaughan[46]), nonleukemic myelosis (Hickling[47]), myelophthisic anemia (Mettier[48]), and agnogenic myeloid metaplasia of the spleen (Jackson, Parker and Lemon[49]). It is probably closely related to or identical with osteosclerotic anemia and in all probability has been confused with myelogenous leukemia, particularly in certain terminal cases of polycythemia vera. As Thompson and Illyne[50] point out, replacement of the bone marrow by various foreign tissues, such as fibrosis, new bone and carcinoma may result in the above hematologic findings, which are chiefly characterized by a few myelocytes, a disproportionate number of normoblasts and reduced platelets. Jackson, Parker and Lemon point out the slow progressive character of the disorder, the average duration in 10 cases studied being 10.8 years. They give prime importance to the splenic abnormality, classifying it as "agnogenic myeloid metaplasia," that is, there is ectopic bone-marrow growth of un-

known or indeterminate origin in the spleen. They rate the bone-marrow findings as of secondary importance. This is contrary to the experience and interpretation of other observers, who agree that the splenic changes are secondary to replacement of bone marrow by abnormal tissue. Emphasis on the splenic changes has led Jackson et al. to conclude that even certain cases of acute or subacute hemolytic anemia with myeloid metaplasia of the spleen are included in this syndrome. Hemolytic anemia is characterized by a very hyperplastic bone marrow and often by bone-marrow activity in other organs; the syndrome described by Vaughan, Hickling, Thompson, Mettier and others presents a bone marrow that is replaced by foreign, usually fibroblastic, tissue. Although the splenic lesions may be similar, it is probable that the conditions are entirely distinct.

Marked splenomegaly, anemia, a moderate elevation in the leukocyte count, myelocytes and nucleated red cells have generally led to the erroneous diagnosis of chronic myelogenous leukemia and to x-ray therapy. This treatment is exactly wrong, since the spleen is apparently trying desperately to fulfill the functions of the replaced marrow. The differential diagnosis from leukemia may be very difficult. It is well to remember that this picture may be the end-result of previous bone-marrow disease, whether polycythemia, osteosclerosis or metastatic malignancy, and that the terminal picture is nonspecific. Only a bone-marrow biopsy by the trephine method will surely settle the diagnosis in most cases. A puncture biopsy usually gives inconclusive results, since the marrow is hypocellular; removal of a button of sternal bone reveals the bone-marrow lesion, which is usually fibrosis, but may show, as Mettier[48] has pointed out in 10 interesting cases, osteosclerosis, Gaucher's disease, carcinomatosis, neurofibromatosis and multiple myeloma. These histologic features are readily distinguished from myelogenous leukemia. X-ray examination of the femurs may show spotty areas of diminished and increased density, and as Vaughan[46] has pointed out, the paucity of the x-ray findings is often surprising in view of the extensive replacement of bone by fibrous tissue, as seen at post-mortem examination.

Polycythemia Vera

This disease of unknown origin is characterized by extensive hyperplasia of the entire bone marrow, with the result that the red cells, leukocytes and platelets become greatly increased in the peripheral blood. The great increase in circulating red-cell mass results in the establishment of a very viscous, slow-moving circulation. The combination of a greatly distended circulation and a tendency to multiple thromboses accounts for the majority of the symptoms of the disorder. These are described by Dameshek and Henstell.[51] These authors point out that the multiplicity of symptoms may result in the diagnosis of psychoneurosis, or if one set of symptoms is outstanding, in such diagnoses as nephritis, cardiovascular disease, migraine or peripheral vascular disease. The blood-platelet count is usually extremely high, and with the sluggish circulation and the increased blood viscosity, thrombotic manifestations are common. These frequently occur in the extremities, simulating thromboangiitis obliterans, but are not infrequently present internally. Thus cerebral thrombosis, coronary thrombosis (Miller[52]) hepatic-vein thrombosis and portal-vein thrombosis may occur. Since many cases go unrecognized for a number of years, being treated for menopause, migraine, heart disease and so forth, it should be the rule to perform a red-cell count — not a Tallqvist hemoglobin — in any patient whose plethoric appearance makes one suspect polycythemia. Further clinical diagnostic aids are distended retinal veins, splenomegaly and hepatomegaly, and flushed mucous membranes. The erythrocyte count usually gives the diagnosis, although in doubtful cases the hematocrit, blood volume and leukocytes and platelet counts are all necessary.

Most patients go along for many years in various degrees of discomfort. The development of the degenerative diseases is accelerated, and death is usually the result of nephritis, coronary disease or a cerebral accident. In 3 of 40 cases which were followed, anemia gradually developed in association with leukocytosis and the presence of immature granulocytes and nucleated erythrocytes. Are these cases of chronic myelogenous leukemia, or do they represent fibrosis of the marrow with myeloid metaplasia of the spleen? Most observers have considered that the polycythemic condition became transformed into leukemia, but it becomes increasingly evident that these cases are not truly leukemic, but that the blood picture is simply leukemoid in type in association with a fibrotic bone marrow and a spleen that is actively attempting to produce bone-marrow cells. It is likely that the majority of the cases of leukoerythroblastic anemia, as pointed out above, have previously been unrecognized examples of polycythemia.

The best treatment for polycythemia is still being debated. X-ray therapy over bones (and marrow) and treatment with phenylhydrazine, Fowler's solution or radioactive phosphorus have all been advocated. Potentially or actually all these methods are dangerous. The induction of an iron-

deficiency state has proved safe and therapeutically effective. Venesections of 500 cc. of blood are performed twice weekly until the hemoglobin is reduced to approximately 80 per cent and the erythrocyte count to approximately 5,000,000. This usually takes from six to eight venesections. The patient is then placed on a low-iron diet, that is, restricted in meats, liver, eggs, green vegetables and rye bread. The combination of a great loss of iron (hemoglobin), together with a continued low intake of iron, results in a sustained iron-deficiency state with relatively low values for hemoglobin. The erythrocyte count under this regime gradually rises to between 7,000,000 and 8,000,000, but with the iron deficiency, the values for hemoglobin, hematocrit and red-cell mass remain low for periods of six to twelve months (average eight months). The method is safe and physiologically sound, and requires but little supervision after the first series of venesections. Estimations of the hemoglobin and hematocrit percentages become of far greater value than the erythrocyte counts.

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Hemophilia

Work on the nature of hemophilia continues to be pursued at the Thorndike Memorial Laboratory in Boston. It was previously shown that the clot-promoting power of normal plasma was present in the globulin fraction of the plasma, from which an extract containing so-called "globulin substance" could be prepared by acid precipitation. More recent work by Lozner and Taylor[53] demonstrated that the effective clot-promoting material was found in plasma euglobulin (plasma proteins insoluble in distilled water, soluble in isotonic saline). It is, of course, hoped that further fractionation will result in the development of an extract effective in the continued treatment of hemophilia, that is, in keeping the blood coagulation time at normal levels. At present, the only definitely effective treatment aside from the topical application of globulin substance is in acute hemorrhage, which is handled either by a transfusion of whole blood or plasma, or by the use of plasma euglobulin.

Brinkhous[54] presents a somewhat different concept regarding the pathogenesis of hemophilia. Studies made by this observer demonstrated that in hemophilic blood the prothrombin was converted to thrombin unusually slowly. This delay in prothrombin conversion could be corrected by adding less than 1 mg. of crude thromboplastin to 100 cc. of the abnormal blood. Brinkhous believes that the beneficial effects of transfusion are due to the addition of thromboplastin, which is derived from cells and platelets. Quick[55] has come to the same conclusion.

Aggeler and Lucia[56] have rendered a valuable service in investigating the potency of a large number (seventeen in all) of so-called "blood-coagulating substances." They found that the claims made for these preparations were, to say the least, greatly exaggerated. Most of them were completely inactive. Only those substances suitable for local use (like certain snake venoms) were at all active. Similar studies are reported by McGavack.[57] In the light of these investigations, the alleged effects of oxalic acid intravenously in the treatment of hemophilia must be greatly discounted. A report on the use of this chemical is that of Page, Russell and Rosenthal,[58] who claim a good effect in 3 cases of hemophilia by the use of repeated intravenous injections of 5 to 10 mg. The actual case reports, however, are quite unconvincing, and it is reassuring that the conclusion is made that "its use, along with other known beneficial measures, *notably multiple transfusions* [italics mine], would be warranted in attempting to control bleeding in hemophilia." McGavack also reports on the use of a substance (Koagmin) similar to oxalic acid in the treatment of hemophilia. This is an extract derived from the weed, shepherd's-purse, and contains dicarboxylic acids. In 4 cases of hemophilia treated with this material prompt shortening of the coagulation time lasted for two to four hours.

An excellent article on certain effects of hemophilia on the growing skeleton is contributed by Caffey and Schlesinger.[59] Simple hemarthrosis, panarthritis and subperiosteal hemorrhage are all carefully considered. An interesting hemorrhagic diathesis with prolonged coagulation time, associated with a circulating anticoagulant, is reported by Lozner, Jolliffe and Taylor.[60] The case differed from hemophilia not only clinically but in certain physiologic respects: a transfusion failed to shorten the clotting time, and normal human plasma and globulin substance were ineffective in vitro. A striking finding was the presence in the blood of a substance interfering with the completion of the normal clotting mechanism. When the patient's plasma was tested in vitro against whole normal blood, clotting was prevented. The circulating anticoagulant might have been in some manner associated with the general lymph-node tuberculosis present.

Purpura

Thrombocytopenic purpura. The pathology of the bone marrow in idiopathic thrombocytopenic purpura has been studied by Limarzi and Schleicher.[61] A uniform finding was marked hyperplasia (increase) of megakaryocytes, with a shift

to young forms; this was particularly striking in the chronic form. Speculation is made regarding the possibility that the spleen in this disease may have an unusual inhibitory effect on platelet production by the bone-marrow megakaryocytes. This is confirmed by some recent unpublished work of Dr. E. B. Miller and myself. Despite the almost complete absence of platelets from the circulating blood, the bone marrow is crowded with megakaryocytes that produce few if any platelets. Directly following splenectomy, there is a striking increase in platelet production by the megakaryocytes, reflected quickly in the peripheral blood by a rapid increase in the platelet count.

On the other hand, Wiseman, Doan and Wilson[62] state that "sternal marrow studies have consistently revealed normal numbers of normal appearing megakaryocytes in a normal cellular setting." They also state that they are convinced, from their supravital studies, that there is increased activity of splenic clasmatocytes in destruction of platelets. In other words, they maintain that the marrow is normal, but the spleen is destroying an increased number of platelets in the disease. As diagnostic essentials of idiopathic thrombocytopenic purpura, Wiseman et al. list: spontaneous purpura with or without free bleeding from the mucous membranes, definite decrease in the blood platelets, normal coagulation and prothrombin times, no unusual anemia or leukocytosis, absence of pathologic cells in both the blood and the marrow, absence of recent history of the ingestion of drugs, and lack of appreciable enlargement of the spleen or lymph nodes. Regarding therapy, x-ray treatment over the spleen is considered worthless, the use of snake venom "has not been encouraging," and parathyroid extract was tried without favorable result. Transfusions help to tide the patient over until either a spontaneous remission becomes established or splenectomy is performed. It is gratifying to note that "full doses" of blood are recommended, in contradistinction to the encomiums of various authors for the use of small transfusions. Why small transfusions should possess any special virtue is a mystery I have never been able to fathom. Splenectomy is the only real cure. In the chronic case, the decision for splenectomy must be made only after repeated observations of the patient's course. The acute cases demand energetic action, which may be summarized as follows: confirmation of the diagnosis by sternal puncture; immediate transfusions; if blood loss persists, splenectomy. Of 9 splenectomized patients, 1 died of postoperative shock, and the others made uneventful recoveries. It has been my experience in several cases that too much temporizing and indecision regarding splenectomy have led to cerebral hemorrhage and death. In the acute case, a quick decision must be made and splenectomy immediately performed, before the patient has had a chance to bleed into vital tissues.

Thrombocytopenic purpura in relation to the menarche is discussed by Goldburgh and Gouley.[63] Pubertal menorrhagia may be the first indication of purpura. Splenectomy is curative and is indicated when repeated transfusions of blood and endocrine therapy have failed to check the hemorrhagic tendency.

Nonthrombocytopenic purpura. Purpura occurs either when the blood platelets become extremely low or when there is damage to the capillary walls. Such cases are divided, respectively, into thrombocytopenic purpura and vascular purpura; in the former the platelet count is low, the bleeding time increased, and the clot retraction poor, whereas in the latter the platelet count is normal, the bleeding time normal or somewhat increased and the clot retraction normal. In both conditions the clotting time is normal and the tourniquet test positive.

Most cases of purpura fall into these two groups. There are rare cases, however, in which, although the platelet count is normal, the platelets themselves are abnormal. These cases may be familial; because of the platelet abnormality, clot retraction is poor and the bleeding time is prolonged. Other familial cases of purpura are probably exaggerated forms of vascular purpura, in which the bleeding time is prolonged although the platelet count, platelet morphology and clot retraction are normal. Bruun,[64] reporting a large family of bleeders, prefers the designation "hereditary hemorrhagic diathesis" for these cases, which have been termed "pseudohemophilia" by von Willebrand[65] and others. In Bruun's cases, a hemorrhagic tendency present in both sexes had been present in four generations and in 15 of 23 members of the family. Four patients had bled to death. The outstanding abnormality was a greatly prolonged bleeding time (over an hour), with normal platelets and a normal platelet count, the tourniquet test being either normal or slightly positive.

A quite benign familial abnormality is described by Davis[66] under the name "hereditary familial purpura simplex." Spontaneous ecchymoses, mostly in women, were the presenting symptom. Diligent examination of the families demonstrated numerous other cases. No hematologic abnormalities were found, the only finding being a positive capillary resistance test in 16 of 25 cases tested. One family also showed hereditary telangiectasia

(Osler-Rendu-Weber disease). Rheumatoid arthritis and rheumatic fever were common in the families studied.

For topical application in cases of vascular purpura and perhaps in other hemorrhagic conditions, including hemophilia in which the bleeding point can be visualized, the use of Russell viper venom (Stypven) has been recommended by Page and Thomas.[67] Pledgets soaked in the solution are applied directly to the bleeding point; all intervening clots or other obstructions must be cleared away. Packing is sometimes advantageous. The venom may also be dropped directly onto the hemorrhagic area from the point of a small-caliber hypodermic needle. Sprays of venom from an atomizer may be used in the nasopharynx or to control bleeding from the uterine cervix. The Russell viper venom appears to accelerate the action of thromboplastic substances and to act with the latter in a synergistic manner.

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Hypoprothrombinemia

The recognition, careful study and treatment of hypoprothrombinemia, or vitamin K deficiency, represent one of the milestones of medical progress of the past decade. The story of vitamin K, its deficiency and its value in clinical medicine is well known. For the interested reader, the review by Quick[55] is recommended. The test that has proved of greatest value in determining the prothrombin time is that of Quick.[68] An important advance in performance of the test, as described by Souter, Kark and Taylor[69] is the preparation of a stable thromboplastin. This is a lyophilized rabbit-brain extract that can be kept indefinitely. Before use it is suspended in salt solution.

Vitamin K deficiency may develop in conditions other than obstructive jaundice: inadequate dietary, particularly of fats, impaired gastrointestinal digestion, unusual loss of fats from the bowel and severe hepatic damage. Prolonged dietary deficiency as a cause of hypoprothrombinemia is emphasized by Kark and Lozner.[70] In the 4 cases studied, multiple deficiencies were present (scurvy, subclinical pellagra), thus offering further evidence that nutritional deficiency in man is rarely, if ever, confined to a single factor. In newborn infants a potential hypoprothrombinemia is probably usually present, and in some infants a hemorrhagic tendency associated with excessively low prothrombin values may be present. Quick and Grossman[71] found that the prothrombin concentration of infants' blood, nearly normal at birth, drops abruptly during the first few days of life, and then usually recovers rapidly. The quick recovery is thought to be due to the establishment of the normal bacterial flora in the intestines, with resultant initiation of the synthesis of vitamin K. Hemorrhagic disease of the newborn is due to a delayed restoration of the prothrombin level. Although the condition may be very severe, it is promptly cured by the oral administration of vitamin K. Poncher and Kato[72] describe a micromethod for the determination of prothrombin, and report on the treatment of 22 infants with hypoprothrombinemia. The average prothrombin time of 10 patients before treatment was 210 seconds (normal, about 25 seconds), and in 12 other patients was more than 300 seconds. Synthetic preparations of vitamin K were administered either orally, intramuscularly or subcutaneously. A therapeutic effect was present within two to six hours. Transfusions were not necessary. Shettles, Delfs and Hellman[73] make the important observation that the plasma-prothrombin level of the newborn infant can be increased not only by feeding vitamin K concentrate directly to the infant after birth, but by administering it to the mother prior to delivery. The values obtained with maternal administration are often three times those normally seen, and in general are higher than can be attained by administering vitamin K concentrate to the newborn infant.

The treatment of vitamin K deficiency is becoming much simpler with the elaboration of numerous synthetic products, some of which may be given parenterally. Kark and Souter[74] report on the treatment of 18 patients with hypoprothrombinemia by the parenteral administration of a water-soluble derivative of 2-methyl,1,4-naphthoquinone. Within a few hours of the intravenous or intramuscular administration of the material, the bleeding was satisfactorily controlled and the prothrombin time was normal. On the other hand, 12 patients with hypoprothrombinemia associated with hepatic disease did not respond to intensive parenteral administration. Thus, if the prothrombin time of a patient with jaundice fails to become normal after treatment, it is evident that hepatic disease is present and the prognosis poor. Andrus and Lord[75] administered 2-methyl, 1,4-naphthoquinone dissolved in corn oil intramuscularly. Single injections intramuscularly of as little as 2 mg. in 2 cc. of oil restored the plasma prothrombin level by as much as 48 per cent, an effect that became evident within eight hours after injection and might be prolonged for as long as a week.

Splenic Disease

Very little that is new has been reported during the past year on this subject. The pathogenesis of so-called "Banti's disease" is discussed by

Thompson[76] on the basis of 137 well-studied cases falling into the general category. It was found that the condition resulted from a variety of primary lesions that produce splenic-vein hypertension. The conclusion is made that the syndrome is a secondary mechanical congestive splenomegaly and that there is no reason for assuming the presence of an unknown toxic agent or for retaining the concept of three stages in the development of Banti's disease. Cirrhosis of the liver exists only as one of several obstructive mechanisms (it was present in 68 per cent of the cases); if it is not present at the time of splenectomy, it will not develop subsequently. The splenic histology is the same in all types. Extrahepatic lesions responsible for congestive splenomegaly, which is suggested as a better term than Banti's disease, are thrombosis of the portal or splenic veins and compression of the splenic vein (in infants and children).

A somewhat different interpretation of the Banti syndrome is that of Ravenna,[77] who believes that the condition is a "fibrocongestive splenomegaly." Although this author concludes that the condition is due largely to splenic congestion, he suggests that this may be caused by "primary" lesions of the small splenic arteries that regulate the flow of blood into the spleen, with secondary portal hypertension. That the Banti syndrome cannot be clinically differentiated from cases of cirrhosis of the liver in which portal hypertension is definitely primary is not discussed. It seems that the views of Thompson and his coworkers adequately explain the pathogenesis of the great majority of the cases, although it cannot be denied that an occasional case may be better explained by Ravenna's thesis.

The removal of very large spleens is discussed by Henry,[78] who has had considerable experience in the tropics. It is emphasized that splenectomy in these cases frequently results in a relaxation of the diaphragm caused by "loss of the cushion on which it has long been moulded and stretched." It is well known that chest complications are frequent following splenectomy, and to obviate these effects, Henry recommends the use of a rubber balloon attached to a source of carbon dioxide and left in place under the diaphragm in the splenic bed after removal of the spleen. The balloon may be gradually deflated and removed after a few days.

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

ANTE-MORTEM AND POST-MORTEM RECORDS AS USED IN WEEKLY CLINICOPATHOLOGICAL EXERCISES

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

CASE 27171

PRESENTATION OF CASE

First Admission. A fifty-eight-year-old garageman entered the hospital complaining of weakness, dizziness, exertional dyspnea and numbness in the fingers.

Two years before admission he noticed slight discomfort around and below his umbilicus, which occurred half an hour after meals and was worse in the morning. This was followed by nausea without vomiting, and gradual subsidence of the symptoms by the next mealtime. Eighteen months before admission numbness and aching appeared in the calves during activity, and the patient found it necessary to watch his feet while walking and lost his balance when his eyes were closed. One year prior to entry dyspnea on exertion developed, and some time later he suffered from transient soreness of the gums and hard palate. Six weeks before admission marked the onset of weakness, lethargy and inability to concentrate, and a sensation of "pins and needles" appeared in the hands and feet, with "deep bone" soreness and swelling of the feet. The numbness and cramps in his legs and feet increased and often awakened him at night; relief could be obtained only by exercise. The patient had not lost more than 7 pounds in weight.

The family history was irrelevant. Fourteen years before admission the patient had had an attack of epigastric pain and jaundice and was told that he was anemic. At forty-five he had had three attacks of gonorrhea in rapid succession. No occupational hazard could be elicited. Although his diet seemed adequate the patient ate very little meat.

On examination the patient was well developed and well nourished and in no apparent distress. The skin had a sallow lemon tint, with questionable icterus of the scleras. The mucous membranes were pale, and the tongue thick and smooth, with atrophy of the papillas. There was cardiac enlargement, and a soft blowing apical systolic murmur; the blood pressure was 120 systolic, 60 diastolic. Pitting edema of the feet and ankles was present, and muscle tenderness in the calves. The knee jerks were hyperactive; vibration sense was diminished at the ankles, but position sense was fairly good in the great toes. The gait was ataxic, with a positive Romberg sign.

The temperature was 99.5°F., the pulse 93, and the respirations 22.

The urine was normal. The blood showed a red-cell count of 1,230,000 with a hemoglobin of 40 per cent, and a white-cell count of 3850 with 60 per cent polymorphonuclears; the platelets were diminished. The red cells showed pronounced poikilocytosis, anisocytosis and some polychromatophilia, with many large cells well filled with hemoglobin. The serum van den Bergh was slightly above normal, the icteric index 7. The serum proteins were 6.1 gm. per 100 cc., and the chlorides were equivalent to 109 cc. N/10 sodium chloride. A blood Hinton test was negative. Gastric analysis revealed achlorhydria.

A gastrointestinal series was negative.

The patient was given intramuscular liver injections and a high-vitamin, high-calorie diet. The reticulocytic response was satisfactory, and he improved symptomatically, being discharged to the Out Patient Department three weeks after admission, when the red-cell count was 3,590,000, and the hemoglobin 60 per cent.

Second Admission (five years later). The patient was followed in the Out Patient Department for two years, where he was given intramuscular injections of liver extract once a week, the red-cell blood count remaining around 4,500,000, with a hemoglobin of 80 per cent. For the next two years he made his own oral preparation according to recipe, but for more than a year before admission he had had no liver preparation whatever, and made little effort to include it in his diet. One month before admission, dizziness, weakness, dyspnea, and numbness in the fingers returned and increased so that once again he came to the hospital.

Physical examination was as before, including the neurologic findings and peripheral edema. The upper border of the liver was at the sixth space, while the lower border was percussed three fingerbreadths below the costal margin in the midclavicular line.

The blood showed a red-cell count of 1,770,000 with a hemoglobin of 54 per cent, and a white-cell count of 1800; the platelets were reduced. The red cells showed poikilocytosis, anisocytosis and macrocytosis. The serum van den Bergh was 2.1 mg. per 100 cc., biphasic, and the nonprotein nitrogen 32 mg. The stools were normal.

A gastrointestinal series showed the folds of the stomach to be widened. Arising from the greater curvature and posterior wall of the antrum of the stomach was a broadly based, slightly lobulated

tumor mass, approximately 2.5 cm. in width. An electrocardiographic recording showed normal rhythm with a rate of 100 and a PR interval of 0.15 second; P waves were not visualized well in Leads 1 and 2, and there was a tendency to left-axis deviation.

On gastroscopic examination the mucosa throughout the stomach was very pale and smooth, but normal to large rugae were present and the blood vessels were not seen shining through the mucosa. In the antrum there appeared to be a smooth nonulcerated polypoid mass. The patient remained in the hospital for three weeks and made a good response to intramuscular injections of liver extract.

Third Admission (ten days later). The patient remained at home, then returned to the hospital. An operation was performed three days after admission, following two 500-cc. blood transfusions.

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Differential Diagnosis

Dr. Wyman Richardson: This is a typical story of pernicious anemia with combined system disease. The most interesting feature develops toward the end of the story and concerns the nature of the gastric tumor.

The history is quite consistent with pernicious anemia, and all the symptoms can be explained on that basis. Whether the nausea without vomiting can be explained on that basis alone is perhaps not certain. I think it probably should be explained in that way.

". . . and was told that he was anemic." I am going to leave that and not come back to it. It could have been the onset of pernicious anemia fourteen years previously but more likely had nothing to do with his illness. The tongue was thick, and one does not usually get a thick tongue in pernicious anemia — it is usually in iron-lack anemia that the tongue is thick and boggy.

The argument whether or not patients with combined system disease can be improved is often raised. Symptomatically they do improve with massive doses of liver extract. I believe that it is wise to give these patients a crude preparation of liver by mouth, as well as parenteral liver. There have been pathologists who argue that you cannot get improvement in combined system disease because the pathological findings are inconsistent with any reversible change; but given a patient with symptoms, one does not know what the disease of that cord is. I am sure you can get improvement in central-nervous-system symptoms with liver, and in the early stages the changes are reversible. I think it is true that the longer the symptoms exist the less likely they are to improve, and I know it is true that ataxia is much easier to treat than spasticity.

A strange thing about patients with pernicious anemia in relapse is that they get frightfully stubborn. You can talk to them and explain the whole situation. However, following treatment they feel so well they say, "Perhaps that doctor was wrong. I shall stop liver and see what happens." They stop, and they get worse. Finally the old symptoms return. Then they get stubborn and think of every conceivable reason why they are going downhill rather than the obvious one — that they are not getting liver. It is always dangerous to stop liver for the purpose of discovering whether patients actually need to continue it. It is necessary sometimes but requires great care in follow-up.

May we look at the x-ray films?

Dr. James R. Lingley: I cannot add to the report in the record. The films show this mass arising from the greater curvature, starting about 5 cm. above the pylorus. The mass is sharply defined and slightly lobulated, and there is some spasm of the antrum but no definite rigidity of the lesser curvature. It is larger than the usual polyp and more consistent with cancer.

Dr. Richardson: Dr. Benedict, do you want to say anything in regard to the gastroscopy in addition to what I have read?

Dr. Edward B. Benedict: The mucosa was smooth and pale, but the blood vessels were not visible, a finding that is an indication that the mucosa was not really atrophic. Very likely the absence of complete atrophy was because the patient had had liver therapy. The polypoid mass was smooth and round; one could not be sure whether it was an adenoma or cancer.

Dr. Richardson: The problem of whether or not this lesion was malignant is absolutely impossible to solve clinically, and may even be difficult for Dr. Mallory. In the first 100 cases of pernicious anemia that we studied here after liver therapy was begun, there were 4 patients in whom we found polyps, and if Dr. Benedict had been here with his gastroscope, we should have undoubtedly found more. I do not know where he would put the incidence of polyps in the stomach with Addisonian anemia, but I should think it would be around 15 or 20 per cent. Is that high?

Dr. Benedict: I have no figures, but I should think that is a little high.

Dr. Richardson: It is my impression that in the old days before liver therapy those patients who had remissions and relapses with no specific therapy developed polyps in much larger proportion than our patients do now. If a fairly high percentage of patients with pernicious anemia develop polyps, and if a fairly high percentage of the polyps become malignant, then one would expect that carcinoma would develop frequently in per-

nicious anemia. In my experience, however, it is rare to find carcinoma in a patient who has definite pernicious anemia. Of course one may see secondary types of macrocytic anemia with a widespread cancerous involvement of the stomach. I think, therefore, that when these patients with pernicious anemia are treated with liver the mucous membrane improves in its general consistence, and polyps no longer develop. This man probably would not have developed a tumor if he had maintained his liver intake.

Is this tumor malignant? I am going to guess that it is not, but there is no real basis for making a guess. One other point, I question the advisability, — and Dr. Sweet will perhaps disagree with me on this, — if one is contemplating a fairly radical gastric operation, of giving two 500-cc. blood transfusions preoperatively in a patient who presumably has had time to restore his blood volume and blood level to normal. Is it not taking an unnecessary risk? May you not get a transfusion reaction, not necessarily due to incompatibility, that will make the postoperative course more stormy than it need be?

Dr. Richard H. Sweet: I agree with that absolutely. When the blood is up to normal, I see no indication for transfusion. We see reactions not infrequently, and I have seen some lately, especially in patients with an anemia. They occur with properly grouped bloods, and no adequate explanation has been found for them. Although we always postpone the operation in such a case, I have never known such a reaction to be responsible for postoperative difficulties.

Dr. Richardson: I thought that you might operate in a period before the reaction occurred, because many are delayed.

Dr. Sweet: That is correct, and I do not like to transfuse my patients and operate immediately. I usually do it two or three days ahead of time.

Dr. Richardson: To summarize, I think this is a case of Addisonian anemia in a patient who eventually developed a polyp in the stomach; the polyp was removed and I hope it will prove to be benign, that is, without any malignant degeneration.

Dr. Benedict: I do not quite agree with what you say in regard to the incidence of malignant degeneration. In a study of adenomatous polyps of the stomach, Dr. Allen and I* found that 40 per cent became malignant. In this particular patient I thought that the adenoma was of such a size it probably was malignant. I have seen quite a number of patients with pernicious anemia and carcinoma, and believe that all patients with pernicious anemia should have gastrointestinal series and gastroscopic examinations at frequent intervals.

Dr. Richardson: Even when they have had adequate treatment?

Dr. Benedict: Yes.

Dr. Richardson: I do not believe that. Have you any figures?

Dr. Benedict: No.

Dr. Tracy B. Mallory: There are a number of studies accumulating which tend to show that patients who eventually develop carcinoma of the stomach have had gastric anacidity for years. On this basis it has been argued that a persistent anacidity in a young person may be considered a strong indication that that patient is likely to develop cancer of the stomach.

Clinical Diagnoses

Pernicious anemia.
Carcinoma of the stomach.

Dr. Richardson's Diagnoses

Pernicious (Addisonian) anemia, with combined system disease.
Adenomatous polyp of stomach (benign ?).

Anatomical Diagnosis

Polypoid carcinoma of the stomach.

Pathological Discussion

Dr. Mallory: Gastric resection was done, and an obvious tumor was found in the stomach. It did not look in the resected specimen very much as it does in the x-ray films. There it seemed to be a definitely polypoid tumor, projecting a considerable distance into the lumen of the stomach. We found a distinctly flat, wide lesion. It did not look particularly polypoid. Post-mortem relaxation of the gastric musculature, particularly, I suspect, of the muscularis mucosae, is the probable explanation. The base was not detectably indurated. On microscopic examination, beginning sharply at each edge of the polyp, the glandular tissue was markedly atypical. The cells were rapidly growing, with many mitotic figures, and the nuclei were hyperchromic and quite disorientated. Cytologically there could be no doubt that the tissue was malignant. Throughout most of the tumor there was no sign of invasion, but in the center of one section we did find a definite spot of invasion extending only 1 mm. below the muscularis mucosae. Therefore, this is not merely carcinoma in situ but has to be regarded as established cancer.

Dr. Richardson: I agree that patients with

*Benedict, E. B. and Allen, A. W. Adenomatous polypi of the stomach. *Surg., Gynec. & Obst.* 58:79-84, 1934.

pernicious anemia should be studied for carcinoma, but what I rather question is, If they are adequately treated, must one then feel obliged to continue gastrointestinal x-rays at frequent intervals?

DR. BENEDICT: I think that these patients should be followed by x-ray studies and by gastroscopy at least three times a year. Perhaps you would say that the patients with pernicious anemia and cancer whom I have in mind were not adequately treated with liver, but they were under observation in this hospital by good men.

CASE 27172

PRESENTATION OF CASE

A fifty-two-year-old woman entered the hospital complaining of nausea and vomiting of two days' duration.

Six months before admission the patient first noticed slight vaginal bleeding occurring at irregular intervals. She consulted her physician, and a biopsy was taken of the cervix, which was reported as carcinoma. Following this diagnosis the patient was given twenty x-ray treatments at another hospital and remained well until two months before admission, when she began to suffer from frequency, incontinence and severe burning during and immediately following urination. Bladder irrigations gave some relief, but occasionally she noticed small blood clots in the urine and gradually an aching pain developed in her entire pelvis and upper thighs. A cystoscopic examination one week before admission was said to have revealed involvement of the bladder by tumor. The patient had always been troubled by constipation, but this had increased appreciably during the last two months and blood occasionally appeared in the stools. Two days before admission persistent nausea, vomiting and obstipation appeared, but there was no pain or abdominal distention.

Twelve years before admission the patient had had a supravaginal hysterectomy for leiomyomas. Her father had died at seventy-two of cancer of the bowel.

The patient was in no apparent distress, but was pale with a questionable icteric tint to the skin and scleras. The heart and lungs were normal; the blood pressure was 130 systolic, 80 diastolic. There was a healed suprapubic surgical incision; the abdomen was soft, with moderate suprapubic tenderness. Rectal examination was negative.

The temperature, pulse and respirations were normal.

The urine showed a ++ test for albumin, and the sediment contained 15 white cells and 2 red cells per high-power field, with many bacteria; a culture yielded an abundant growth of alpha-hemolytic streptococci. The blood showed a red-cell count of 4,100,000 with 8.9 gm. of hemoglobin (photoelectric-cell technic), and a white-cell count of 10,500. The nonprotein nitrogen of the blood serum was 17 mg. per 100 cc., and the chlorides 99.9 milliequiv. and the carbon dioxide combining power 23.1 milliequiv. per liter; a serum van den Bergh was normal, and the blood Hinton reaction negative. Examination of the stools was negative.

A plain x-ray film of the abdomen showed a large amount of gas and fecal material in the colon. There were some gas-filled loops of small bowel in the midabdomen, but these were not dilated.

During hospitalization the patient was drowsy, and became nauseated and vomited from time to time; satisfactory bowel movements were obtained with the help of enemas. Gradually her urinary output dropped, and two weeks after admission the nonprotein nitrogen was 100 mg. per 100 cc., and the chlorides 102 milliequiv. per liter. She developed uremic twitchings and anuria. Finally drowsiness deepened to coma, and the signs of bronchopneumonia appeared. Death occurred three weeks after admission.

DIFFERENTIAL DIAGNOSIS

DR. RICHARD CHUTE: Here we have a fifty-two-year-old woman with carcinoma of the cervix, proved six months previously. At that time she was given twenty x-ray treatments at another hospital, presumably of 200 to 300 r apiece, so that we may guess she received a total of 4000 to 6000 r, focused on the carcinoma of the cervix. That would be enough to cause a regression of the disease, but in most cases would not be enough to destroy the carcinoma completely. Therefore, in my opinion, the carcinoma was arrested but probably not destroyed. Four months afterward,—two weeks before admission,—she had frequency, incontinence and burning, and noticed some small blood clots in the urine. Cystoscopic examination a week before admission was said to have revealed extension of the tumor into the bladder, a happening which is frequent in carcinoma of the cervix. She noticed pain in the pelvis and upper thighs, which would also suggest extension of the tumor into the tissues of the pelvis. Blood occasionally appeared in the stools; this suggests the possibility that the rectum had been invaded by the carcinoma, but rectal examination later on was negative, and one examination of the stools was negative, so that I am going to guess that this blood was due to hemorrhoids, not to rectal involvement.

The supravaginal hysterectomy for leiomyomas twelve years before probably had nothing to do with the present picture, except that it is too

bad that the cervix was not also taken out at that time. There was a family history of carcinoma. Two days before admission, that is, six months after her trouble began and several months after the x-ray therapy, nausea, vomiting and obstipation appeared, but no pain or abdominal distention. When she came in she had a moderate secondary anemia. It is said that she had a questionable icteric tint to the skin, but later on the van den Bergh test was reported as normal, so that I doubt the jaundice. The urine showed some blood, which would be consistent with involvement of the bladder with tumor—a few pus cells and alpha-hemolytic streptococci are fairly frequently found in the urinary tract and usually do not have serious pathological significance. The nonprotein nitrogen, the chlorides and the carbon dioxide combining power were essentially normal.

The patient was drowsy, nauseated and vomited from time to time, and her abdomen was somewhat distended at the end. Gradually the urinary output dropped. Two weeks after admission the nonprotein nitrogen had risen to 100 mg. per 100 cc. and she developed uremic twitching and anuria, dying from what I suppose was uremia, with terminal bronchopneumonia.

Jaffe, Meigs, Graves and Kickham* have shown that a great proportion of patients with carcinoma of the cervix die in uremia from obstruction of the ureters. This is usually due to tumor growth, or to tumor that has been fibrosed by radiation therapy. Sometimes the constriction of the ureters is entirely due to fibrosis following radiation therapy, without any tumor tissue's playing a part in producing the constriction. In some cases the carcinoma of the cervix has been completely cured, but ureteral occlusion by postradiation fibrosis has been responsible for death.

It would seem to me that we are dealing in this case with a carcinoma of the cervix that had had inadequate x-ray therapy, and that had extended through the pelvis, involving the bladder and the ureters. Also it is possible that the ureters were constricted purely by fibrosis following radiation therapy, without tumor's playing a part, but my guess is that tumor was actually obstructing them. Therefore, I am going to make a diagnosis of carcinoma of the cervix involving the ureter, with extension to the bladder, bilateral hydroureter and hydronephrosis.

Dr. F. Dennette Adams: May I ask Dr. Chute if he believes that carcinoma of the cervix can be cured by irradiation? He made a distinction between destruction of the tumor and arrest of the disease.

Dr. Chute: I do believe that carcinoma of the cervix can be cured by irradiation therapy, but I do not believe that it can be cured with 4000 to 6000 r delivered through the skin by an x-ray machine.

Dr. Adams: But do you believe it can be cured by irradiation?

Dr. Chute: My opinion is that an early carcinoma of the cervix can probably be cured by a combination of radium implantation and external irradiation. Jaffe et al. have shown, however, that some of the patients with cured carcinoma die later on with fibrosis of the ureter.

Clinical Diagnosis

Carcinoma of cervix, with involvement of the bladder, ureters and rectum.

Dr. Chute's Diagnoses

Carcinoma of the cervix, with extension to the bladder and occlusion of the ureters.
Hydronephrosis bilateral.
Hydroureter, bilateral.

Anatomical Diagnoses

Carcinoma of cervical stump, involving the bladder, and obstructing the ureters, with metastases to the right kidney and both lungs.
Vesicovaginal fistula.
Bilateral hydronephrosis, severe on right, slight on left.
Radiation fibrosis.
Septic pulmonary infarcts, multiple.
Old postoperative supravaginal hysterectomy.
Phleboliths.

Pathological Discussion

Dr. Tracy B. Mallory: Dr. Chute has outlined the problem very clearly; it concerned not the underlying disease but the nature of the terminal complications. At autopsy recurrent tumor was found occupying most of the pelvis. This had grown into the bladder and also into the vagina, and one complication which was not foreshadowed clearly by the symptoms was a vesicovaginal fistula. Perhaps the actual perforation did not occur until the patient had become virtually anuric, and for that reason it was not obvious. The lower ends of both ureters were completely surrounded and invaded by tumor. It was impossible to probe them from below, although working from above the probe could be forced through with considerable difficulty. The ureters above the point of

*Jaffe, H. L., Meigs, J. V., Graves, R. C. and Kickham, C. J. E. Ureteral and renal complications of carcinoma of cervix; their classification and management. *Surg., Gynec. & Obst.* 70:178-184, 1940.

obstruction were quite markedly dilated, and when a nick was made into them, urine under tension spurted out. Both kidneys showed a slight dilatation of the pelvis. The right kidney was normal in size. The left kidney weighed only 75 gm., which is more than an ordinary anatomic variation and probably means a considerable atrophy. I should therefore imagine that the obstruction had developed sooner on the left than on the right. The terminal pulmonary complication was one of multiple septic infarcts. There were also, however, a certain number of nodules of tumor in the lungs.

A PHYSICIAN: Was the mucous membrane of the rectum involved?

DR. MALLORY: No; we found no mechanical explanation for the obstipation. There were numerous adhesions within the abdomen, and one loop of ileum was firmly adherent to the dome of the bladder, a rather common complication in some of these heavily irradiated cases. The mucosa was normal and showed no signs of irradiation necrosis. There was another adhesion to the old laparotomy scar, but no kinking about either lesion. I do not believe that the patient had any actual obstruction.

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ILL FARES THE LAND

Current events have at last made it apparent, by the very monotony of their repetition, that in this century it is impossible for a nation to live within itself like a walled town, shut away from the outer world. The nation that tries to escape from the reality outside finds that reality comes and pounds on its gates. We are ourselves finally facing this fact, but only within a very few months have we come definitely to admit it.

The questions for which we have had to find the answers have been whether security can be bought with money or by success in barter and trade, or whether it can be purchased by the reactionary policies of appeasement. History has not only answered these questions for us in the negative, but has actually given us every reason to doubt whether the average human being has ever had any reason to consider personal security a normal condition of life.

A great deal has been said about security in the last few years. The favored classes of this nation took economic security for granted in the lush years before 1917, and all classes anticipated it during the years of the inverted pyramid prior to 1929. After the financial debacle, it was one desideratum of living: a peaceful, strifeless security with a tight roof, oil heat, a radio by the fireplace and a policeman on the corner to keep away evildoers.

The trouble with this security, as we are learning now, is its vulnerability. It is too dependent on peace on earth to men of good will. Everything must run smoothly to make it effective. Too many disturbances can take place to interfere with its serenity, and the only protection against them is to be equipped to handle them. When there are wolves around, the armed hunter, despite the risks of the chase, is more secure than the peaceful shepherd with his flock.

Security, of an individual or of a nation, is not a passive condition. It is the reward only of an alert, aggressive attitude, and when that spirit of aggressiveness falters and fades away, no sense of security can survive it for very long. The final protection against highwaymen does not lie in fast coach horses for escape, or in paying tribute to them, but in seizing them and dealing with them, with justice, but without mercy.

Security without effort, for the individual or the nation, is transitory and ephemeral. It is as undesirable as it is unreal. We have given ourselves over too much to the thought of security as being part of the natural condition of living. We have emphasized its importance in the life of the child. We have associated it with protective tariffs, high interest rates and iron-bound annuities, not realizing that we had completely missed its definition; it is not the accompaniment of an arrived millennium, but the reward of valor, of strength and of watchfulness.

Democracy with its institutions has of all forms of government come the closest so far to offering any material number of the earth's inhabitants the

opportunity to achieve and perhaps maintain a degree of security, but we are learning again that it is at the price of eternal vigilance. We may desire the perpetuation of what we consider certain fundamental rights of man, but they are recognized as rights only in a democracy, and we have to be willing to go forth in the defense of them. We have to risk in order to hold; we must sometimes lose in order to gain.

THE PREVENTION OF TETANUS

TETANUS does not rank high as a cause of death or of illness in ordinary times in New England, and its occasional occurrence has been regarded as more or less inevitable. This point of view is changing, and it seems possible that many cases can be prevented by prophylactic active immunization with tetanus toxoid.

Tetanus toxoid, prepared and administered in much the same way as diphtheria toxoid, produces a basic immunity and puts the specific protective mechanism of the body into such shape that it will respond rapidly when needed. In the event of subsequent injury, another injection of tetanus toxoid is followed by a rise in the patient's antitoxin titer high enough to prevent a tetanus infection. Should this injection be omitted through neglect of an apparently trifling injury, and should tetanus infection occur, the latter of itself may start the production of enough antitoxin to promote recovery or even prevent a clinically evident intoxication. Such at least is the rationale of active immunization against tetanus, and its theoretical basis is sound.

Experimental proof for this theory, at least so far as human beings are concerned, was not available until the current war produced injuries in quantity. Available data for the French army, where immunization was compulsory, and for the British army, where it has been extensively used, indicate that tetanus has been completely prevented in immunized persons. Most, if not all, of the credit for this has been ascribed to the use of toxoid.

Prophylactic administration of tetanus antitoxin, with the attendant serum reactions and sensitization to serum, appears to be unnecessary in persons who have been actively immunized with toxoid.

The desirability of active immunization of troops seems beyond reasonable doubt. What of its use in civilian practice? Certainly those persons running more than the usual risk of exposure might well be immunized. In this group are veterinarians, hostlers, horsemen in general and farmers. Possibly children should also be placed in this category, for their risk of traumatic injuries is high. Persons already sensitive to horse serum might well consider immunization, to avoid the chance of allergic reactions following prophylactic doses of antitoxin. If the incidence of tetanus has been high in the civilian war-wounded, immunization of the general population should be considered in areas that are potential zones of attack.

The choice of an immunizing agent is still unsettled. Both fluid and alum-precipitated preparations have their advocates, and there are some advantages — without apparent disadvantages — in employing tetanus toxoid combined with diphtheria toxoid or typhoid vaccine. Reactions to tetanus toxoid are, on the whole, infrequent and mild; and their occurrence should tend to lessen as experience in manufacture and administration is increased.

Because of the present small number of cases and the cost of wholesale immunization, the prevention of tetanus with toxoid does not appear to be a problem to be dealt with by public-health officials. Practicing physicians, however, should advocate immunization, particularly for the groups mentioned above.

MEDICAL EPONYM

HENOCH'S PURPURA

Professor Eduard Heinrich Henoch (1820–1910) discussed "Ueber eine eigenthümliche Form von Purpura [A Peculiar Form of Purpura]" before the Berlin Medical Society on November 18, 1874. His paper appeared in the *Berliner klinische Wochenschrift* (**11**: 641–643, 1874). He had reported a single case six years previously. A portion of the translation follows:

The characteristic feature is the combination of purpura with marked intestinal symptoms. The latter manifest themselves in the form of colic, abdominal tenderness, vomiting (frequently of masses of green material) and bloody evacuations. Further, there were rheumatoid pains in all our cases, except one, including swelling of the joints in one case. Characteristic, too, was the occurrence of these symptoms in recurrent attacks at intervals of a week or more so that in the average case three to seven weeks elapsed, and in one case more than three months, before the final end of the process.

R. W. B.

MASSACHUSETTS MEDICAL SOCIETY

PROPOSED CHANGES IN THE BY-LAWS

Through an oversight, the following proposed changes in the by-laws, which were approved by the Council at its meeting held on February 5, 1941, and were published in the February 27, 1941, issue of the *Journal*, were omitted from the list of proposed changes enclosed with the preliminary program recently forwarded to all members of the Society. A notice to this effect has been forwarded to each member, and a leaflet containing the additional changes will be distributed at the annual meeting of the Society.

AMENDMENT 16. Amend the first paragraph of Chapter IV, Section 1, to read:

The Council shall consist of councilors chosen by the district societies, and the president, ex-presidents, president-elect, vice-president, vice-presidents *ex officiis*, secretary and treasurer of the general society, secretaries of the district societies, and the chairman of each standing committee.

AMENDMENT 17. Amend the first paragraph of Chapter IV, Section 3 to read:

The Council at its annual meeting, on nomination by the Nominating Committee and/or from the floor, shall elect by ballot officers of the Society as follows: president-elect, who shall serve as president-elect until the annual meeting of the Society next ensuing after his election and shall become president on his installation in the course of that meeting, serving thereafter as president until the next following annual meeting and the installation of his successor; a vice-president, secretary and treasurer, all of whom shall assume the duties of office at the close of the annual meeting of the Society and shall hold office until their successors have been duly elected; except only that at the annual meeting of the Society in 1941 there shall be nominated and elected a president to serve for that year.

In the absence of a president-elect, the Council, at its next annual meeting, shall upon nomination by the Nominating Committee and/or from the floor, elect a president. Councilors only shall be eligible to the offices above named. Upon nomination by the Nominating Committee, the Council shall elect by ballot a fellow to deliver an oration at the annual meeting of the Society the following year.

AMENDMENT 18. Change Chapter VI, Section 3, to read:

The President-Elect shall assist the President in the performance of his duties in such a manner as the President may direct and in so doing shall be considered to represent the President.

AMENDMENT 19. Change Sections 3, 4 and 5, Chapter VI to Sections 4, 5 and 7, respectively.

ROBERT N. NYE, *Secretary* pro tempore.

COMMITTEE ON STATE AND NATIONAL LEGISLATION

House Bill 1222, the bill to establish a separate board of registration for chiropractors was given "leave to withdraw" by the Committee on Public Health on April 15; this report was accepted by the House the next day, but will have to be accepted by the Senate, before it is finally disposed of.

HENRY C. MARBLE, *Chairman*.

SECTION OF OBSTETRICS AND GYNECOLOGY*

RAYMOND S. TITUS, M.D., *Secretary*
330 Dartmouth Street
Boston

DEATH FOLLOWING MISMANAGEMENT OF DELIVERY

A thirty-four-year-old primipara who had received no prenatal care was sent to a state institution about a week before her expected date of delivery.

The past history was entirely irrelevant. She had never had scarlet fever or kidney trouble.

Physical examination on admission was normal. The heart was not enlarged; there were no murmurs. The lungs were clear and resonant; there were no rales. The blood pressure was 130 systolic, 80 diastolic. The abdomen was the size of a full-term pregnancy, and the fetal heart was heard. There was considerable edema of both legs. The urine showed a large amount of albumin. There was no record of the patient's weight. She was put to bed and treated for mild toxemia.

Six days after entrance, labor started spontaneously. It was said that at the end of twelve hours the cervix was fully dilated. The position was a posterior vertex, and the head was thought to be in the mid-pelvis. Under ether anesthesia a high-forceps delivery was attempted, without success; another physician attempted version, which likewise failed. Following these two operative procedures, a third consultant was called to decide

*A series of selected case histories by members of the section will be published weekly. Comments and questions by subscribers are solicited and will be discussed by members of the section.

whether a cesarean section should be performed. This was decided against because the patient was in such poor condition. She died a few hours later, undelivered.

Comment. No comment is really necessary. Although this patient had no prenatal care, her death cannot be attributed to her own neglect. There is no excuse for such obstetrics. It is only fair to say that no obstetrician saw this patient. Until the obstetrics that is done in all hospitals, including state as well as private and incorporated institutions, is adequately supervised, an occasional repetition of this disaster is unavoidable.

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MEDICAL POSTGRADUATE EXTENSION COURSES

The following sessions, given by the Massachusetts Medical Society in co-operation with the Massachusetts Department of Public Health, the United States Public Health Service and the Federal Children's Bureau, have been arranged for the week beginning April 27:

BRISTOL SOUTH (Fall River Section)

Tuesday, April 29, at 4:30 p.m., at the Union Hospital, Fall River. Pediatric Case Discussions. Instructor: R. Cannon Eley. Howard P. Sawyer, *Chairman.*

HAMPDEN

Wednesday, April 30, at 4:00 p.m., at the Academy of Medicine, Professional Building, 20 Maple Street, Springfield, and at 8:00 p.m., in the Outpatient Department of the Skinner Clinic, Holyoke Hospital, Holyoke. Recent Advances in Medical Therapeutics. Instructor: Charles L. Short. Alfonso A. Palermo, *Chairman.*

WORCESTER

Tuesday, April 29, at 8:30 p.m., in the Nurses' Home of the Milford Hospital, Milford. Infections of the Hands and Feet. Instructor: William E. Browne. Joseph Ashkins, *Chairman.*

APPLICANTS FOR FELLOWSHIP

Owing to an error, the following names were omitted from the list of applicants for fellowship printed in the April 10 issue of the *Journal.*

HAMPDEN DISTRICT

McELLIGOTT, MAURICE JAMES, Westfield State Sanatorium, Westfield.
Rush Medical College, University of Chicago, 1937.

Wayne C. Barnes, *Secretary.*

PLYMOUTH DISTRICT

GOLDSTEIN, WALTER, 169 West Elm Street, Brockton.
University of Berlin, 1923.

MATHEWS, MOLYNEAUX PAUL, 28 Maple Avenue, Brockton.
Middlesex University School of Medicine, 1933.

Ralph C. McLeod, *Secretary.*

DEATHS

McCARTHY — THOMAS H. McCARTHY, M.D., of Brockton, died April 11. He was in his seventy-eighth year.

Dr. McCarthy received his degree from the Harvard Medical School in 1890. He was on the surgical staff of the Brockton Hospital at the time of his death. He held memberships in the Massachusetts Medical Society and the American Medical Association.

PACKARD — LORING B. PACKARD, M.D., of Brockton, died April 12. He was in his sixty-fifth year.

Born in Sharon, he attended Yale University and received his degree from Harvard Medical School in 1903. After two years at the Boston City Hospital, he became resident surgeon at the Haymarket Relief Station, Boston. In 1912 he became superintendent of the Brockton Hospital, which capacity he filled until his retirement in 1919. At the time of his death he was on the staff of the Brockton Hospital as surgeon and roentgenologist.

Dr. Packard was a member of the Massachusetts Medical Society, the American Medical Association and the New England Roentgen Ray Society.

MISCELLANY

MAINE NEWS

MAINE MEDICAL ASSOCIATION

The annual meeting of the Maine Medical Association will be held at the Marshall House, York Harbor, on June 22, 23 and 24.

The following physicians have been recently admitted to membership in the Maine Medical Association:

Everett F. Conlogue, Fairfield.
Paul A. Jones, Union.
William B. O'Sullivan, Biddeford.
L. Dean Webber, Kittery.

THAYER HOSPITAL, WATERVILLE

Staff meetings are held at the Thayer Hospital, Waterville, at 7:30 p.m., on the first, second and fourth Thursdays of every month from September to May, inclusive (the Kennebec County Medical Association meets on the third Thursday of every month). In addition to clinical case studies, panel discussions and guest speakers are included in certain of the programs. Dr. Arnold P. Meiklejohn, of the Thorndike Memorial Laboratory, Boston City Hospital, will speak on "Vitamin Therapy" at the May 1 meeting. Dr. Samuel A. Levine, of Boston, will speak on "Some Important Errors in Cardiac Diagnosis" at the May 22 meeting. The profession is cordially invited to attend these meetings.

PANEL DISCUSSIONS

The following panel discussions, with the names of the chairmen, are available to the county medical societies in 1941:

Coronary Disease. Dr. E. H. Drake, Portland.
Complications of Pregnancy. Dr. R. B. Moore, Portland.
Diseases of the Liver and Bile Passages. Dr. J. Gottlieb, Lewiston.
Endocrine Dysfunction. Dr. J. Carswell, Camden.
Syphilis. Dr. O. R. Johnson, Portland.
Chemotherapy. Dr. F. T. Hill, Waterville.
Appendicitis. Dr. I. M. Webber, Portland.

NOTICES

BOSTON MEDICAL HISTORY CLUB

The next meeting of the Boston Medical History Club will take place at the Boston Medical Library, 8 Fenway, Boston, on Monday, April 28, at 8:15 p.m. Dr. Iago Galdston, secretary, Medical Information Bureau, New York Academy of Medicine, will speak on "Humanism and Public Health."

All interested persons are cordially invited to attend.

HENRY JACKSON LECTURE

The Henry Jackson Lecture for 1941, under the auspices of the New England Heart Association, will be given on Friday, May 2, at the Boston Medical Library at 8:15 p.m. Commander J. R. Poppen, M.D., Navy Department, Bureau of Aeronautics, Washington, D. C., will discuss "Cardiovascular Problems in Aviation Medicine."

Interested physicians and medical students are cordially invited to attend.

JOSEPH H. PRATT DIAGNOSTIC HOSPITAL

Bennet Street, Boston
Lecture Hall, 9–10 a.m.

MEDICAL CONFERENCE PROGRAM, MAY

Thursday, May 1 — Epidemiologic Field Trip to Halifax. Dr. J. H. Dingle.
Friday, May 2 — Pancreatic Disease and Enzyme Analysis in Early Life. Drs. Sidney Farber and Charlotte Maddock.
Tuesday, May 6 — Pneumoencephalography. Dr. Kurt Goldstein.
Wednesday, May 7 — Urticaria. Dr. E. A. Brown.
Thursday, May 8 — Hospital case presentation. Dr. S. J. Thannhauser.
Friday, May 9 — Marked Hyperthyroidism. Dr. Oliver Cope.
Tuesday, May 13 — Subacute Bacterial Endocarditis with Special Reference to Treatment. Dr. J. M. Faulkner.
Thursday, May 15 — Some of the Effects of Flying on the Cardiovascular System. Dr. Ashton Graybiel.
Friday, May 16 — Early Diagnosis of Carcinoma of the Stomach. Dr. B. B. Crohn.
Tuesday, May 20 — Clinicopathological conference. Drs. C. S. Keefer and H. E. MacMahon.
Thursday, May 22 — Extrarenal Azotemia. Dr. Emanuel Ginsburg.
Friday, May 23 — Some Current Problems in Gastrointestinal Surgery. Dr. Richard Warren.
Tuesday, May 27 — Secretin Test of Pancreatic Function. Dr. A. S. Hartwell.
Thursday, May 29 — X-ray demonstration. Dr. Alice Ettinger.

On Wednesday and Saturday mornings throughout the month, with the exception of May 7, Dr. S. J. Thannhauser will give a medical clinic on hospital patients.

SUFFOLK DISTRICT MEDICAL SOCIETY

The annual meeting of the Suffolk District Medical Society will take place on Wednesday, April 30, at 8:15 p.m., at the Boston Medical Library.

PROGRAM

Short History of Eclampsia. Dr. Robert M. Green.
Symposium on Pre-eclamptic Toxemia and Eclampsia. Drs. Burton E. Hamilton, Arthur T. Hertig, Maurice B. Strauss, George van S. Smith, Duncan E. Reid, George C. Prather and Raymond S. Titus (chairman).

There will be a business meeting at 8:00 p.m. for election of officers and the report of the society for 1940.

NEW ENGLAND OBSTETRICAL AND GYNECOLOGICAL SOCIETY

The spring meeting of the New England Obstetrical and Gynecological Society will be held in Providence, Rhode Island, on Wednesday, May 14. Registration will be held at the Providence Lying-In Hospital, 50 Maude Street, Providence. Two programs will run concurrently in the morning: one beginning at 9:00 at the Providence Lying-In Hospital and consisting of inspection of the hospital and a dry clinic; the other at the Rhode Island Hospital beginning at 8:00 with an operative clinic and followed by a symposium on cancer and a dry clinic. Luncheon at 12:30 will be served at the two hospitals.

The afternoon program will commence at 1:30 at the Providence Lying-In Hospital, with a meeting of the executive committee, a symposium on hydatidiform mole and chorioepithelioma, and the presentation of papers. A general meeting of the society will follow at 4:15, with a reception and dinner at the Squantum Club at 5:30.

MIDDLESEX SOUTH DISTRICT MEDICAL SOCIETY

The annual meeting of the Middlesex South District Medical Society will be held at the Hotel Continental, Cambridge, on Wednesday, May 14.

PROGRAM

11:30 a.m. Business meeting.
12 m. Annual Oration: Middlesex South and Massachusetts medicine. Dr. Harold G. Giddings.
12:45 p.m. Luncheon.

CONSULTATION CLINICS FOR CRIPPLED CHILDREN IN MASSACHUSETTS, UNDER THE PROVISIONS OF THE SOCIAL SECURITY ACT

CLINIC	DATE	CLINIC CONSULTANT
Lowell	May 2	Albert H. Brewster
Haverhill	May 7	William T. Green
Brockton	May 8	George H. Van Gorder
Gardner	May 13	Mark H. Rogers
Worcester	May 16	John W. O'Meara
Pittsfield	May 19	Frank A. Slowick
Northampton	May 21	Garry deN. Hough, Jr.
Fall River	May 26	Eugene A. McCarthy
Hyannis	May 27	Paul L. Norton

HAMPDEN DISTRICT MEDICAL SOCIETY

The annual meeting of the Hampden District Medical Society will be held on Tuesday, April 29, at Hotel Kimball, Springfield, at 4:00 p.m. Dr. H. Edward MacMahon, professor of pathology, Tufts College Medical School, will speak on "Clinical and Morphologic Findings in Bright's Disease." Dinner will be served at 6:30 p.m. at the expense of the society.

ANNUAL CONCERT OF THE BOSTON DOCTORS' SYMPHONY ORCHESTRA

The Boston Doctors' Symphony Orchestra will give its second annual concert on Sunday, May 11, at 8:15 p.m.

in Jordan Hall. Alexander Thiede will conduct. Dr. Werner Mueller will appear as soloist.

Proceeds of the concert will be used for the establishment of a fund for a free bed in each of the following hospitals: Beth Israel Hospital, Children's Hospital, Massachusetts Eye and Ear Infirmary and Boston Dispensary. Tickets at $1.00 may be obtained by applying to Dr. Julius Loman, Pelham Hall Hotel, Brookline (BEA 2430).

AMERICAN ASSOCIATION FOR THE STUDY OF GOITER

The next annual meeting of the American Association for the Study of Goiter will be held at the Hotel Statler, Boston, on May 12, 13 and 14. The program for the three-day meeting will consist of papers dealing with goiter and other diseases of the thyroid gland, dry clinics and demonstrations.

POSTGRADUATE COURSE IN OBSTETRICS

The Illinois State Department of Public Health and the Children's Bureau, United States Department of Labor, are sponsoring ten 4-week courses in obstetrics at the Chicago Lying-in Hospital during the fiscal year 1941–1942. Only a limited number of physicians will be accepted for each course. The only cost to those taking the course is for room and board and $25.00 ($10.00 of which is refunded at the completion of the course). Applications and inquiries should be addressed to: Postgraduate Course, Department of Obstetrics and Gynecology, 5848 Drexel Avenue, Chicago, Illinois.

SOCIETY MEETINGS AND CONFERENCES

Calendar of Boston District for the Week Beginning Sunday, April 27

Monday, April 28

12:15–1:15 p.m. Clinicopathological conference. Peter Bent Brigham Hospital amphitheater.

*8:15 p.m. Humanism and Public Health. Dr. Iago Galdston. Boston Medical History Club. Boston Medical Library, 8 Fenway, Boston.

Tuesday, April 29

*9–10 a.m. Sir Charles Bell in Modern Dress. Dr. Leonard Carmichael. Joseph H. Pratt Diagnostic Hospital.

12:15–1:15 p.m. Clinicoroentgenologic conference. Peter Bent Brigham Hospital amphitheater.

5 p.m. Hospital Research Council. Massachusetts General Hospital, Ether Dome.

Wednesday, April 30

*9–10 a.m. Hospital case presentation. Dr. S. J. Thannhauser. Joseph H. Pratt Diagnostic Hospital.

*12 m. Clinicopathological conference. Children's Hospital.

4–8 p.m. New England Pediatric Society. Children's Hospital, Boston, and Longwood Towers, Brookline.

8 p.m. Boston Society of Biologists. Harvard Medical School, Amphitheater E.

Thursday, May 1

*9–10 a.m. Epidemiologic Field Trip to Halifax. Dr. J. H. Dingle. Joseph H. Pratt Diagnostic Hospital.

Friday, May 2

*9–10 a.m. Pancreatic Disease and Enzyme Analysis in Early Life. Drs. Sidney Farber and Charlotte Maddock. Joseph H. Pratt Diagnostic Hospital.

*8:15 p.m. Cardiovascular Problems in Aviation Medicine. Dr. J. R. Poppen. Henry Jackson Lecture. New England Heart Association. Boston Medical Library, 8 Fenway, Boston.

Saturday, May 3

*9–10 a.m. Hospital case presentation. Dr. S. J. Thannhauser. Joseph H. Pratt Diagnostic Hospital.

*Open to the medical profession.

April 25 — Massachusetts Society for Social Hygiene. Page 708, issue of April 17.

April 25 — Salem Tumor Clinic. Page 579, issue of March 27.

April 26 — boston City Hospital Alumni Day. Page 708, issue of April 17.

April 28–30 — American Academy of Physical Medicine. Scientific session. Page 579, issue of March 27.

April 30 — Waltham Medical Meeting. Page 708, issue of April 17.

May 1–29 — Joseph H. Pratt Diagnostic Hospital, Medical Conference Program. Page 752.

May 5–9 — American Association of Industrial Physicians and Surgeons and American Industrial Hygiene Association. Page 484, issue of March 13.

May 8 — Pentucket Association of Physicians. Page 263, issue of August 15.

May 11 — Boston Doctors' Symphony Orchestra. Second annual concert. Page 752.

May 12–14 — American Association for the Study of Goiter. Notice above.

May 13–16 — National Gastroenterological Association. Hotel Commodore, New York City.

May 14 — New England Obstetrical and Gynecological Society. Page 752.

May 21, 22 — Massachusetts Medical Society, Boston.

May 28–June 2 — American Board of Obstetrics and Gynecology. Page 262, issue of February 6.

May 29–31 — Medical Library Association. Page 671, issue of April 10.

May 30, 31 — American Heart Association. Hotel Statler, Cleveland.

May 30–June 2 — American College of Chest Physicians. Hotel Statler, Cleveland.

June 2–6 — American Medical Association. Cleveland.

June 22–24 — Maine Medical Association. Marshall House, York Harbor, Maine.

October 14–17 — American Public Health Association. Page 579, issue of March 27.

District Medical Societies

ESSEX NORTH

May 7 — Page 708, issue of April 17.

ESSEX SOUTH

May 14 — Relation of the Doctor to the Law. Mr. Leland Powers. New Ocean House, Swampscott.

FRANKLIN

May 13 — This meeting will be held at 11 a.m. at the Franklin County Hospital, Greenfield.

HAMPDEN

April 29 — Page 752.

MIDDLESEX SOUTH

May 14 — Page 752.

NORFOLK

May 8 — Censors' meeting. Hotel Puritan, Boston.

SUFFOLK

April 30 — Page 752.

May 1 — Censors' meeting. Page 261, issue of February 6.

WORCESTER NORTH

April 23 — Eighty-second annual meeting. Page 709, issue of April 17.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Techniques of Conception Control. By Robert Latou Dickinson, M.D., and Woodbridge Edwards Morris, M.D., general medical director, Birth Control Federation of America. A practical manual issued by the Birth Control Federation of America, Incorporated. 4°, paper, 56 pp., with 50 illustrations and 3 tables. Baltimore: Williams and Wilkins Company, 1941. 50c.

Atlas of Electroencephalography. By Frederic A. Gibbs, M.D.; and Erna L. Gibbs. F°, cloth, 221 pp., with 18 figures and 102 plates. Cambridge, Massachusetts: Lew A. Cummings, 1941. $7.00.

Merchants in Medicine. By Emanuel M. Josephson, M.D. 8°, paper, 23 pp. New York: Chedney Press, 1941. $1.50.

A Diabetic Manual: For the mutual use of doctor and patient. By Elliott P. Joslin, M.D., Sc.D., clinical professor of medicine emeritus, Harvard Medical School, medical director, George F. Baker Clinic, New England Deaconess Hospital, and consulting physician, Boston City Hospital. Seventh edition, thoroughly revised. 8°, cloth, 238 pp., with 53 illustrations and 24 tables. $2.00.

Natural Resistance and Clinical Medicine. By David Perla, M.D., instructor in medicine, Columbia University College of Physicians and Surgeons; and Jessie Marmorston, M.D., assistant in pathology, Cornell University Medical College. 4°, cloth, 1344 pp., with 44 tables. Boston: Little, Brown and Company, 1941. $10.00.

That None Should Die. By Frank G. Slaughter, M.D. 8°, cloth, 423 pp. New York: Doubleday, Doran and Company, Incorporated, 1941. $2.75.

Applied Physiology. By Samson Wright, M.D., F.R.C.P., John Astor Professor of Physiology, University of London Middlesex Hospital Medical School, and examiner in physiology, University of Leeds. Seventh edition. 8°, cloth, 787 pp., with 367 illustrations. New York: Oxford University Press, 1940. $7.00.

The Medical Clinics of North America. Vol. 25, Number 2. March, 1941: Baltimore Number. 8°, cloth, 303 pp., with 21 illustrations and 9 tables. Philadelphia: W. B. Saunders Company, 1941. $2.67.

Studies from The Rockefeller Institute for Medical Research. Reprints, Vol. 117. 4°, paper, 606 pp., with 127 tables and 128 illustrations. New York: The Rockefeller Institute for Medical Research, 1941. $2.00.

Science and Seizures: New light on epilepsy and migraine. By William Gordon Lennox, M.D., Sc.D. (hon.), assistant professor of neurology, Harvard Medical School, and visiting neurologist, Boston City Hospital. 8°, cloth, 258 pp., with 10 illustrations. New York: Harper and Brothers, 1941. $2.00.

BOOK REVIEWS

A Textbook of Medicine. Edited by Russell L. Cecil, M.D., Sc.D. Fifth edition, revised and entirely reset. 8°, cloth, 1744 pp., with 173 illustrations. Philadelphia and London: W. B. Saunders Company, 1940. $9.50.

When a textbook of medicine reaches its fifth edition it is fair to assume that its worth is established and that it may take rank with the best in American medical literature. This treatise is a summary of present-day medicine by one hundred and thirty-five American authors, each one an authority in his field. That so many participate in this work is due to the fact, in the words of the editor, "that the rapid growth of medical science during the last few years has made it almost impossible for a single individual to master the entire field." It is a fine demonstration of the high standard of internal medicine in America. Still one misses the personality of the individual master that is found in works like Osler's *Practice of Medicine.*

Introduction to Medical Biometry and Statistics. By Raymond Pearl, Sc.D., Ph.D., LL.D. Third edition, revised and enlarged. 8°, cloth, 537 pp., with 121 illustrations, and 140 tables. Philadelphia and London: W. B. Saunders Company, 1940. $7.00.

Statisticians are familiar with the early editions of this work and will welcome this new one, which is a great improvement. For this group the volume is of great value — the chapter on sampling is a masterpiece. The preface gives the impression that the book is for beginners in this field of medicine, but actually it is too advanced for novices. The late Dr. Pearl states that he has omitted "accounts of many of the recent and more recondite mathematical developments of statistical methodology," but he has included too many advanced methods for the physician attempting to obtain a rudimentary knowledge of the subject. Throughout the book are parts that would be exactly what the physician needs, and interspersed are far too advanced ideas. However, no ideal treatment of this subject is available to the physician, and this volume seems the nearest approach. The book could be of great value for the practitioner attempting statistical analysis, if he had the advice of someone with experience in the statistical field in selecting such parts of the book as he should study.

The Virus: Life's enemy. By Kenneth M. Smith, F.R.S. 12°, cloth, 176 pp., with 19 illustrations. New York: Macmillan Company, 1940. $2.00.

The inability to obtain a visual image of the virus long delayed a direct approach to the study of these substances. However, methods were evolved that obviated many of the difficulties, and new vistas have been opened to an understanding of the nature and action of the virus. The author presents an able and concise summary of the fruits of virus research. This should prove an excellent introduction to those who are not in a position to delve into the extensive literature pertaining to these agents, a literature that embraces chemistry and botany as well as epidemiology.

That the two great enigmas of medicine, neoplasms and viruses, may be related is, indeed, intriguing, and data here presented point in that direction. Preoccupied as one may be with the chemotherapeutic achievements recently gained, one must not lose sight of the great importance of the role of the virus disease in man and his environment.

The Histamine and Insulin Treatment of Schizophrenia and Other Mental Diseases. By Horace Hill, M.R.C.P. 12°, cloth, 133 pp. Baltimore: Williams and Wilkins Company, 1940. $1.75.

Of the various types of shock treatment used for schizophrenia, insulin has had the widest use up to recent times. Hill has added histamine to the insulin treatment and believes that the results are better than with insulin alone. In this small book, he gives case reports of 34 patients treated by this method; 12 were considered well at the end of the course of treatment, and 12 others were improved. Most of the patients suffered from schizophrenia, but a number showed signs of involutional melancholia. A detailed report on all the cases is given as an appendix to this brief monograph, and there are various references to the literature. Although this method of treatment has been largely superseded by other methods, Hill's reports will be found of interest to psychiatrists.